Comorbidity and diagnosis of developmental disorders

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This chapter explores two main themes in two separate sections. The first section explores some of the challenges involved in the diagnosis of complex developmental disorders such as specific language impairment (SLI), developmental dyslexia, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). The second section of the chapter will consider the issue of co-morbidity between developmental disorders, and discuss the various models that have been proposed to explain potential overlap.

Part I: Issues in the Diagnosis of Developmental Disorders

Many developmental disorders that affect cognition and behaviour, such as Down syndrome, Fragile X syndrome, and Turner syndrome, have a known genetic basis. Some of these disorders also involve specific physical abnormalities, such as short stature or particular facial features, which are characteristic of a particular disorder. The presence of testable genetic markers and outward physical signs mean that such disorders are relatively straightforward to diagnose. Williams syndrome is a case in point.

Phenotypically, Williams syndrome is characterised by particular physical abnormalities, including facial dysmorphology ("elfin-like" appearance) and heart disease (most commonly, supravalvular aortic stenosis - narrowing of the aorta). Individuals with Williams syndrome typically show "hyper-social" personalities but tend to lack skills in social judgment. On the cognitive level, Williams syndrome is characterised by mental retardation (full-scale IQs usually in the range of 50-60), alongside a somewhat uneven cognitive profile, with relative strengths in expressive language and face processing, and particular weaknesses in visuo-spatial abilities (Karmilloff-Smith, 2008; Martens, Wilson, & Reutens, 2008).

Williams syndrome is caused by a deletion of approximately 26 genes on the long arm of one copy of chromosome 7q11 (Peoples, Franke, Wang, Perez-Jurado, Paperna et al., 2000). Most significantly, 96% of individuals with classic Williams syndrome show a deletion of one ELN allele (Lowery, Morris, Ewart, Brothman, Zhu et al., 1995). The ELN gene codes for elastin, a structural protein found in connective tissue in multiple organs. Hemizygous ELN deletion is thought to result in abnormal elastin production and to ultimately cause the supravalvular aortic stenosis that affects individuals with Williams syndrome. However, given that ELN is expressed only negligibly in the human brain, its deletion is unlikely to account for the cognitive characteristics of Williams syndrome (Frangiskakis, Ewart, Morris, Mervis, Bertrand et al., 1996). Even though ELN deletion cannot completely account for the full Williams syndrome phenotype, it nevertheless provides a useful genetic marker for the disorder.

ELN deletion can be detected using a chromosomal screening technique called fluorescent in situ hybridization (FISH), which utilises fluorescent probes to detect particular DNA sequences. As is true of virtually all developmental disorders, there is considerable variation in the expression of the Williams syndrome phenotype. Some cases of Williams syndrome, in which all the classic clinical signs are clearly apparent, are relatively easy to diagnose on the basis of the clinical phenotype. However, subtler, more difficult-to-diagnose cases in which, for example, facial abnormalities are not obvious or cardiac problems are mild, are not uncommon. FISH screening is particularly useful in such instances and provides an invaluable tool for confirming a diagnosis of Williams syndrome.

The example of Williams syndrome clearly illustrates the importance of genetic screening in the diagnosis of particular developmental disorders. However, such techniques can only be

utilised when disorders have an established genetic basis. Indeed, there are numerous heritable developmental disorders for which genetic basis is yet to be established. For such disorders, diagnoses must be made purely on the basis of phenotypic characteristics. Although the phenotypic characteristics of some developmental disorders may include outwardly observable physical signs, many disorders involve no such diagnostic clues. Thus, diagnoses must be made on the basis of neurobiological, cognitive, or behavioural markers of the disorder. Reading disorder (dyslexia), ADHD, SLI, and ASD are each an example of such disorders. These disorders can be more challenging to diagnose, given that they have no characteristic physical manifestations and no known set of necessary and sufficient genes to allow objective genetic confirmation of a diagnosis.

SLI

SLI is diagnosed among individuals who, despite no frank sensory or neurological dysfunction, and no significant ASD features, achieve scores on standardised tests of language significantly below that expected on the basis of their age and non-verbal abilities. For example, the International Classification of Diseases (ICD-10; World Health Organisation, 1993) specifies that language ability must fall more than 2 *SD*s below that expected for the individual's chronological age and at least 1 *SD* below their non-verbal ability. The SLI consortium (2004) specified that either receptive or expressive language skills should be at least 1.5*SD*s below that expected for chronological age and that non-verbal IQ should be at least 80. In a large epidemiological study of SLI, Tomblin et al. (1997) specified that for a diagnosis of SLI, performance on at least two measures of (receptive or expressive) language should be at least 1.25 SDs below the mean (i.e., a standard score ≤ 80), with non-verbal IQ in the normal range (i.e., ≥ 85).

In reality, SLI is substantially heterogeneous, and has several empirically-derived subtypes defined according to profiles of ability across comprehension and expression, and according to the degree to which phonology, grammar, semantics, and pragmatics are affected (see Leonard, 2000). However, SLI is a useful umbrella term and a substantial proportion (around 50%) of pre-school and school-aged children with SLI present with a common profile of language difficulties, which is characterised by problems in language production and comprehension. Moreover, deficits in phonology and syntax are more severe than are deficits in higher order, lexical, or pragmatic language skills (the so-called "mixed receptive-expressive" subtype; Rapin, 1996; Conti-Ramsden & Botting, 1999).

Although there are differences between studies and between diagnostic manuals in terms of how severely language must be impaired in order to receive a diagnosis of SLI, agreement is almost universal that language ability must be discrepant from non-verbal ability. However, this can create problems for the detection and diagnosis of SLI, and some have questioned the validity of the criteria. Firstly, although language-impaired children with normal NVIQ tend to have better outcomes than language-impaired children with depressed NVIQ (e.g., Bishop & Edmundson, 1987; Stothard et al., 1998), this does not show that the language impairment in the former case is qualitatively different from the language impairment in the latter case. Rather, high NVIQ may allow some children to compensate for their language problems, a route not open to children with low language and low NVIQ.

Second, nonverbal ability appears to decline over time among people with SLI, with several studies reporting a drop in NVIQ of 10 points or more across development (Botting, 2005; Mawhood, Howlin, & Rutter, 2000; Tomblin, Freese, & Records, 1992). Therefore,

receiving a diagnosis of SLI depends, in part, on at what age an individual is assessed. A child may be referred at 5 years of age and have a NVIQ of 85, thus meeting criteria for SLI. If the same child had been referred at 8 years of age, their NVIQ could have dropped to 75 and thus they would not meet criteria for the diagnosis.

Related to both of these issues, language impairment in SLI is highly heritable, but the discrepancy between verbal and non-verbal ability appears not to be (Bishop, North, & Donlan, 1995). In twin studies, the heritability of a given trait (i.e., the proportion of variation in a trait that is accounted for by genes) is established by exploring the relative similarity of identical (monozygotic; MZ) and non-identical (dizygotic; DZ) twins on that trait. The basic logic here is that, for a given trait, the greater the degree of similarity between MZ twins (who share 100% of genes) relative to the degree of similarity between DZ twins (who share only 50% of genes, on average), the greater the contribution of genes to variation in that trait. The size of the difference between MZ and DZ twins is used to calculate the univariate heritability of the trait in question (DeFries & Fulker, 1985, 1988). To illustrate, imagine that one member of an MZ twin pair (the "proband") and one member of a DZ twin pair each has SLI and each score 2*SD*s below the typical mean on a test of language. Now imagine that the co-twin of the MZ proband also scores 2SDs below the mean on the same language test, whereas the co-twin of the DZ proband only scores 1SD below the mean. This would give a heritability estimate for language ability of one (i.e., 100% of the variance in language ability is due to genetic variation). Now, in the twin study of SLI by Bishop et al., the heritability of language scores was very high (indeed, depending on which measure of language ability was used, it was close to one), whereas the heritability of the discrepancy between language scores and scores on a test of nonverbal ability was close to zero. This suggests that reference to NVIQ may not be essential when diagnosing

SLI, given that language impairment has the same etiology in SLI as it does in "non-specific" language impairment.

Given the difficulties associated with defining SLI (and other complex developmental disorders; see below), Bishop (e.g., 2006) has argued that we could "cut loose from conventional clinical criteria for diagnosing disorders and to focus instead on measures of underlying cognitive mechanisms. Psychology can inform genetics by clarifying what the key dimensions are for heritable phenotypes" (p.1153). For the purposes of conducting genetic studies of SLI (and other disorders) and for remediating the core language impairment in the disorder, perhaps defining SLI according to its cognitive endophenotype would be more productive. Generally-accepted criteria for an endophentype (or "cognitive marker") are that it is associated with the disorder in question, is present at all stages of the disorder (even if superficial behavioural difficulties have resolved), is heritable, and is present in non-affected family members at levels greater than would be expected by chance (e.g., Gottesman & Gould, 2003). The most promising candidate for a cognitive marker of SLI is diminished nonsense word repetition (NWR). In a NWR test, the participant listens to non-words spoken by the tester, and repeats each immediately after hearing it. It is well established among typically developing (TD) individuals that NWR skills are strongly associated with structural language ability (Baddeley, Gathercole, & Papagno, 1998; Service, 1992), independent of NVIQ (e.g., Conti-Ramsden, Botting, & Faragher, 2001).

Critically, poor NWR distinguishes children with SLI from TD children in over 80% of cases (Conti-Ramsden et al., 2001) and even characterises "resolved cases" of SLI who receive an early clinical diagnosis, but who perform in the normal range on broad standardised language

measures later in life (Bishop et al., 1996; Conti-Ramsden et al., 2001). Moreover, diminished NWR runs in the families of individuals with SLI (including among non-affected relatives; e.g., Lindgren et al., 2009) and is highly heritable (e.g., Barry, Yasin, & Bishop, 2006). Importantly, the inclusion in molecular genetic studies of NWR as a marker of SLI has become routine, and has led to significant advances in our understanding of the etiology of the disorder (e.g., SLI Consortium, 2002, 2004).

Reading disorder

Reading disorder is diagnosed when an individual's "reading achievement, as measured by individually administered standardised tests of reading accuracy or comprehension, is substantially below that expected given the person's chronological age, measured intelligence, and age-appropriate education" (American Psychiatric Association, 2000). A major difficulty with this definition is that no distinction is drawn between to distinct aspects of reading, namely reading accuracy and reading comprehension. An individual with "reading disorder" may be able to decode only a small fraction of printed words that they are exposed to, but may understand all of the words they can decode. In contrast, an individual might be able to decode the majority of printed material they encounter, but understand very little of the meaning of the material. The former kid of reading disorder is termed developmental dyslexia, whereas the latter is termed reading comprehension impairment. We'll focus our discussion on dyslexia, which is defined by the National Institute of Neurological Disorders and Stroke as,

> "a brain-based type of learning disability that specifically impairs a person's ability to read. These individuals typically read at levels significantly lower than expected

> despite having normal intelligence. Although the disorder varies from person to person, common characteristics among people with dyslexia are difficulty with spelling, phonological processing (the manipulation of sounds), and/or rapid visual-verbal responding"

Using a criterion of scoring more then 2*SD*s below the mean on a measure of reading accuracy, plus normal IQ, Rutter et al. (2004) found that between 3% and 6% of children in the UK could be classified as having dyslexia. However, as with the diagnosis of SLI, relying on discrepancy scores (in this case between IQ and reading ability) may obscure the underlying problem in dyslexia. Indeed, there is little evidence that greater gains in reading accuracy are made by poor readers with high IQ than poor readers with low IQ (e.g., Hatcher & Hulme, 1999). Nonetheless, as with SLI, it is possible to diagnose dyslexia on the basis of objective performance on standardised measures. Diagnosis of two disorders we consider next are rather more complicated.

ADHD

ADHD is defined as a "persistent pattern of inattention and/or hyperactivity–impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development" (American Psychiatric Association, 2000). Specifically, a diagnosis requires that an individual shows six or more signs of inattention (e.g., not listening when spoken to directly; being forgetful in daily activities), hyperactivity/impulsivity (e.g., fidgeting; blurting out answers before questions have been completed), or both, for a period of at least six months. Three subtypes of ADHD have been identified: predominantly inattentive; predominantly hyperactive-impulsive; and combined inattentive/hyperactive-impulsive.

ADHD is diagnosed largely on the basis of behavioural signs. This is challenging not only because of the subjective nature of making judgements about behaviour, but also because ADHD features characteristically fluctuate over time and across contexts (see Hulme & Snowling, 2009). Thus, a single behavioural assessment at one time point in one setting is insufficient for making a diagnosis; information from multiple sources must be obtained. Diagnostically relevant information is typically gathered through direct observation at school, at home, or in a clinical setting, as well as through the reports of parents, teachers, and the affected individual. Detailed semi-structured parental interviews, such as The Parental Account of Children's Symptoms (Taylor, Schachar, Thorley, & Wieselberg, 1986), may be used. Information may also be gathered by asking the parent, teacher, or child themselves to complete standardised questionnaires, such as the Strengths and Difficulties Questionnaire (Goodman, 1997), which involves items that focus on ADHD-relevant aspects of behaviour (e.g., "Restless, overactive, cannot stay still for long: not true/somewhat true/certainly true").

The fact that behavioural reports and clinical observations are inherently subjective – opinions can potentially vary considerably between parent, teacher, clinician, and the individual themselves – is a limitation in current diagnostic methods. Such difficulties have prompted researchers to try to identify reliable cognitive markers that may potentially be used to aid diagnosis of ADHD. For example, executive dysfunction has been suggested as a possible candidate. Executive function is an umbrella term for a set of abilities, related to frontal lobe functioning, which are involved in the flexible control of action by allowing disengagement from the immediate environment (see part II, below, for further discussion). It is clear is that children with ADHD perform poorly on certain tasks (especially those assessing inhibitory control and working memory) that fall under the umbrella of executive

functioning (e.g., Stuss & Knight, 2002), and performance on these tasks is associated with severity of ADHD features (e.g., Thorell & Wåhlstedt, 2006). Moreover, recent evidence suggests that executive dysfunction in ADHD meets a further criterion for an endophenotype/cognitive marker, in that unaffected family members also appear to show diminished executive functioning (Gau & Shang, 2010). It is not yet clear that executive dysfunction meets the remaining criteria for a cognitive marker of ADHD, but this finding is nevertheless promising. Indeed, it is possible that tests of executive functioning may eventually be used routinely in the differential diagnosis of ADHD.

ASD

The Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV; American Psychiatric Association, 2000) identifies five discrete "pervasive developmental disorders": (1) autistic disorder; (2) Rett's disorder; (3) childhood disintegrative disorder; (4) Asperger's disorder; and (5) pervasive developmental disorder not otherwise specified (PDDNOS). According to DSM-IV, autistic disorder (autism) is characterised by impairments in three discrete domains: qualitative impairment in social interaction (e.g., poor eye contact; lack of social or emotional reciprocity); qualitative impairment in communication (e.g., delay or lack of spoken language; failure to initiate or sustain conversation); and restricted repetitive and stereotyped patterns of behaviour, interests, and activities (e.g., motor mannerisms; inflexible adherence to specific, non-functional routines or rituals).

However, the validity of the pervasive developmental disorder categories has been called into question. Research shows that they cannot be reliably distinguished from each other, and

presentation is unstable over time. For example, in our view, there is no conclusive evidence for any qualitative difference in the presentation or outcome of intellectually high-functioning autistic disorder and Asperger's disorder (e.g., Macintosh & Dissanayake, 2004). Indeed, the only distinction between these two diagnostic categories is the age at which first words/phrases were spoken, a feature is not core to the syndrome. Moreover, studies have shown that many children who meet PDDNOS criteria at one time point meet autistic disorder criteria at a later time point (Eaves & Ho, 2004; Stone, Lee, Ashford, Brissie, Hepburn et al., 1999). These issues have been recognised by many researchers for a number of years. Indeed, following Wing and Gould (1979), many have started to take a more dimensional view, widely adopting the term, "autism spectrum disorder" to encompass autistic disorder, Asperger's disorder, and PDDNOS. This research is now being acknowledged by the American Psychiatric Association (2011), which has suggested that DSM-IV pervasive developmental disorder distinctions can be considered "equivalent to trying to 'cleave meatloaf at the joints'". Thus, a series of proposed changes, to be implemented in DSM-V, have recently been published online (American Psychiatric Association, 2011).

DSM-V will adopt the new category "autism spectrum disorder" (ASD), which will subsume each of the pervasive developmental disorders listed in DSM-IV, except for Rett's syndrome. Most notably, the three domains of impairment that previously characterised autistic disorder in DSM-IV will be reduced to two, which will be used to diagnose ASD: (1) social-communication impairments (which must include deficits in social-emotional reciprocity, nonverbal communicative behaviours used for social interaction; and in developing and maintaining relationships, appropriate to developmental level); and (2) fixated interests and repetitive behaviours (which must include at least two of the following: stereotyped or

repetitive speech, motor movements, or use of objects; excessive adherence to routines, ritualized patterns of verbal or nonverbal behaviour, or excessive resistance to change; highly restricted, fixated interests that are abnormal in intensity or focus; hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment). This change reflects implicit recognition that social and communicative abilities are inextricably linked, which potentially poses a challenge to those researchers who claim that the genes underlying each aspect are different (Ronald, Happé, Bolton, Butcher, Price et al., 2006). Rather than different genes contributing to two *components* of ASD (social abilities and communicative abilities), it seems more logical, perhaps, to suggest that multiple genes underlie one *aspect* (social-communication).

For a number of reasons, ASD is one of the most challenging developmental disorders to diagnose. Although a small proportion of ASD cases can be attributed to specific genetic syndromes such as Fragile X syndrome or tuberous sclerosis, the majority of ASD cases are idiopathic (arising from unknown causes). Although there is substantial evidence that the disorder has a (largely, but not exclusively) genetic basis (see Rutter, 2005) molecular genetic studies have, thus far, failed to establish a set of necessary and sufficient genes that underlie ASD. However, molecular genetic studies have begun to identify a set of genes that are reliably associated with the disorder (International Molecular Genetic Study of Autism Consortium, 1998, 2001, 2005). Despite this recent progress, we are a long way from possessing any genetic/biological test for ASD. Moreover, there are, as yet, no clear cognitive or neurobiological markers of the disorder.

Given the lack of clear markers for ASD, the disorder can currently only be diagnosed on the basis of its behavioural characteristics. A number of standardised instruments have been

developed to aid in the diagnosis of ASD for clinical and research purposes. These include checklists/questionnaires, observational schedules, and structured interviews. Checklists/questionnaires such as the Social Responsiveness Scale (Constantino, 2002) and the Social Communication Questionnaire (Rutter, Bailey, Berument, Le Couteur, Lord et al., 2003) are usually completed by an informant (typically a parent or teacher), and generally stipulate a certain threshold, scores above which are said to be indicative of ASD. They have the advantage of being quick and cheap to administer. However, they rely on the judgements of untrained individuals who may have limited knowledge of whether particular behaviours should be considered normal or abnormal. Such measures are extremely useful in screening for ASD or for research purposes, but they cannot be used in isolation to establish a clinical diagnosis.

In clinical settings, it is considered good practice to use both an observational instrument and a parental interview to gain an insight into current behaviour, as well as developmental history. The most widely used observational instrument is the Autism Diagnostic Observation Schedule- Generic (ADOS- G; Lord, Risi, Lambrecht, Cook, Leventhal et al., 2000). The ADOS-G is a semi-structured, standardized assessment of communication, social interaction, and play/imaginative use of materials. It consists of four alternative modules, each of which is designed for individuals with particular verbal abilities and developmental level. ADOS-G diagnostic algorithms are based on DSM-IV and ICD-10 criteria and have thresholds for autism (autistic disorder) as well as broader ASD. However, the ADOS-G assesses social and communication impairments only – not restricted repetitive and stereotyped patterns of behaviour. Thus, the ADOS cannot be used without additional diagnostic checks. Given this limitation, the ADOS-G is frequently used alongside another standardised diagnostic tool, the Autism Diagnostic Interview-Revised (ADI-R; LeCouteur,

Lord, and Rutter, 2000). The ADI-R is a semi-structured interview conducted with a parent, consisting of 93 items, which focus on behaviours relating to the three domains of impairment set out in DSM-IV.

The ADOS-G and ADI-R are frequently heralded as the "gold standard" tools for diagnosing ASD. However, each has significant disadvantages over other tools. One of the most significant limitations of the ADI-R concerns the development of the diagnostic algorithm. As Bishop (2011, May 30) points out, rather than using statistical analyses to establish a set of items that most accurately distinguishes between individuals with and without ASD, the algorithm items were simply selected on the basis of their match to clinical descriptions of ASD. This means that poorly discriminating items could unknowingly be included in the algorithm, leading to inaccurate diagnoses in complex/borderline cases. This raises serious questions about whether the ADI-R in its current form should be used in either clinical or research settings. Indeed, it is not clear that the ADI-R is a better diagnostic tool than shorter, cheaper alternatives that require no special training (unlike the ADI-R). For example, Berument, Rutter, Lord, Pickles and Bailey (1999) found that the Autism Screening Questionnaire, a 40 item questionnaire that takes just a few minutes to complete, was just as discriminating as the ADI-R.

In addition to the concerns raised above, the ADOS-G and ADI-R have been shown to have a surprisingly low specificity. In the largest study of its kind (involving around 1500 cases), Risi, Lord, Gotham, Corsello, Chrysler et al. (2006) found that, if used in isolation, the specificity of each measure was less than 50%. Indeed, they each identify around 29% of non-spectrum children as having autism. If used together, specificity is improved, but in over

15% of cases the instruments disagree on spectrum vs. non-spectrum diagnoses. Ultimately, in many cases, therefore, an ASD diagnosis comes down to expert clinical judgment.

Part II: Comorbidity Between Developmental Disorders

In medicine, the term "comorbidity" was originally introduced to describe situations where two discrete diseases or disorders co-occur concurrently or across time (Feinstein, 1970). Applying this concept to the case of developmental psychopathology yields some striking statistics. Between 1/3 and 1/2 of all children/adolescents with a primary diagnosis of ADHD have a comorbid conduct disorder or oppositional defiance disorder (e.g., Anderson, Williams, McGee, & Silva, 1987). Some 13% of those with ADHD have a comorbid major depressive disorder and approximately the same percentage have an anxiety disorder (e.g., Velez, Johnson, & Cohen, 1989). Among children/adolescents with a primary diagnosis of major depressive disorder, between 1/3 and 1/2 have a comorbid anxiety disorder (e.g., Costello, Farmer, Angold, Burns, & Erkanli, 1997). Among individuals with ASD, some 70% have at least one comorbid disorder (most commonly social anxiety disorder), and over 40% have two or more such disorders (Simonoff, Pickles, Charman, Chandler, Loucas, & Baird, 2008). This list could be extended significantly, but is sufficiently long to illustrate the point that comorbidity in developmental psychopathology is apparently the rule, rather than the exception. Such high levels of comorbidity between developmental/psychological disorders have led some to question whether the term can be meaningfully applied in this field, and indeed in any field outside of somatic medicine (e.g., van Praag, 1996, 2000). The extent of comorbidity in developmental psychopathology may call into question whether the current diagnostic systems laid down in the DSM-IV and ICD-10 can maintain the notion that psychopathology consists of discrete disease entities. Alternatively, there may exist discrete disorders, but the boundaries between them are not accurately drawn by the current

diagnostic systems (Maj, 2005). Regardless, it is widely accepted that there are multiple competing explanations for comorbidity (see Neale & Kendler, 1995). In this chapter, we will focus on what we take to be one of the most important issues in this debate. This issue concerns whether comorbidity is real in a given case, or whether it is merely apparent or superficial. Put another way, the issue concerns whether the disorder identified as comorbid (e.g., social anxiety disorder) with the primary diagnosis (e.g., ASD) really represents the same clinical entity (with the same underlying causes) as that diagnosed in isolation from the primary diagnosis. This issue is captured perfectly by Maj (2005, p.183) in his discussion of the relation between panic disorder and schizophrenia:

> "But are we sure that the occurrence of panic attacks in a person with schizophrenia should be conceptualised as the 'comorbidity of panic disorder and schizophrenia'? Is the panic of someone with agoraphobia, of a person with major depression, and of a person with schizophrenia the *same* psychopathological entity that simply 'co-occurs' with the other three?" (emphasis added)

In this example, it would be of great importance for our understanding of agorophobia, schizophrenia, and depression, for their diagnosis and for their clinical management, if the same "panic disorder" was associated with each disorder. However, if superficially similar presentation of panic across the disorders has a different underlying cause in each case (i.e., if the similarity in panic across the disorders is only apparent and does not reflect "panic disorder" in each case), then describing panic disorder as comorbid with each disorder not only distorts our understanding of the primary disorders themselves, but could also lead to the employment of ineffective forms of treatment to remediate the panic associated with each. Bishop (2010) uses the term "phenomimicry" to describe the situation where the causes of one disorder (e.g., schizophrenia) produce signs/features that resemble those of a separate disorder (e.g., panic disorder). Unlike the more common term "phenocopy", which refers to

an environmentally-caused disorder resembling a genetically-caused disorder, the term phenomimicry does not make assumptions about etiology, so we will continue to use this term throughout the chapter.

In order to establish empirically whether any two apparently co-occuring disorders are truly co-morbid, or whether one of the two is merely a phenomimic of another disorder, one needs to dig below the surface of behaviour, and explore the underlying causes and correlates of behavioural impairment at the levels of cognition, neurobiology, and genetics (Morton & Frith, 1995; Morton, 2004). Thus, disorders can potentially be comorbid at the levels of cognition, neurobiology and/or genetics. In our view, however, what is not sufficient from an empirical perspective (even if it may be justified from a clinical perspective), is to claim comorbidity merely on the basis of similarity in behavioural presentation of disorders. Quite simply, there are many different possible causal routes to the same behaviour, and so it is imprudent to assume that superficially similar behavioural presentations reflect the same clinical entity. Although the causal chain between genes and behaviour, via neurobiology and cognition, are undoubtedly complex and multifactorial, it seems reasonable to suggest that if comorbidity between disorders is real rather than apparent, then the signs/features of the disorder in that instance (e.g., social anxiety in people with ASD) have at least partially the same causal route as they do in the case of someone receiving a single diagnosis (i.e., social anxiety disorder in the absence of ASD). The search for causal pathways within and across developmental disorders is essential and we hope will be the focus of intense research activity in coming years.

Below, we will discuss two prominent cases where comorbidity between developmental disorders has been postulated. The first case concerns the relation between ASD and SLI. The second case concerns the relation between ADHD and developmental dyslexia. These cases provide an interesting contrast because, in our view, the former case is substantially more likely to represent an example of phenomimicry than the latter case. The point in this discussion is not to draw firm conclusions about comorbidity in either case, but to highlight the kind of evidence and critical analysis that is useful in coming to a decision about whether comorbidity is real or apparent.

The Case of Language Impairment in ASD: Comorbid SLI or Phenomimic of SLI?

Around half of individuals with ASD manifest a clinically significant impairment in structural language (phonology/grammar/semantics), and this impairment can occur independently of any diminution of nonverbal IQ (NVIQ; e.g., Baird, Simonoff, Pickles, Chandler, Loucas et al., 2006). In this way, language impairment in ASD can resemble SLI, which has led some to suggest that the two disorders are fundamentally related, and that language impairment in ASD represents comorbid SLI (e.g., Tager-Flusberg, 2004). Thus, according to this model, language-impaired individuals with ASD (henceforth ALI) have inherited both ASD and SLI (i.e., ALI = ASD + SLI). This model has been challenged by some researchers, who argue the available evidence suggests that language impairment in ASD is merely a phenomimic of SLI (e.g., Williams, Botting, & Boucher, 2008; Whitehouse, Barry, & Bishop, 2008). The debate regarding comorbidity between the two disorders continues abound. As discussed above, to answer any question regarding comorbidity, we need to dig below surface behaviour and explore the cognitive, neurobiological, and etiological causes of language impairment in each disorder[1].

Neuro-cognitive underpinnings

When discussing cognition, we mean the mental operations or functions of the brain. Unlike neurobiology or behaviour, cognition is not directly observable, but has to be inferred from patterns of behaviour. However, as Morton (2004) points out, cognition is not merely a re-description of behaviour. It provides a mechanism for understanding and explaining behaviour, and leads to specific predictions that can be tested empirically.

Several cognitive theories of SLI have been built on the basis that poor performance on certain cognitive tasks serves as a clinical marker for SLI. As discussed above, the majority of individuals with SLI perform at least 1.25*SD*s below the typical mean on tests of nonsense word repetition (NWR) and grammatical tense marking (Rice, Wexler, & Cleave,1995). The test performance itself is merely an example of behaviour (Morton, 2004), but the specific *patterns* of difficulty shown by individuals with SLI on these tasks (or specific profiles of performance on different tasks) are suggestive of the underlying cognitive deficit in the disorder. For example, the seminal finding that difficulty with NWR is seen only when items are 3 syllables or more in length (along with the finding that most children with SLI have a reduced digit span) fuelled the hypothesis that SLI results primarily from an underlying deficit in short-term memory (Gathercole & Baddeley, 1990). This theory has been challenged by other results, such as the finding that it is not just the length of the items to be repeated (i.e., the amount of material to be stored in short-term memory), but also the structure of the items. Hence, Marshall and van der Lely (2009) recently found that children with SLI found it disproportionately more difficult to repeat consonant clusters that were located medially in a nonsense word (e.g., *ka**dr**epa*), as opposed to at the beginning of the

word (e.g., ***dr****epaka*). Marshall and van der Lely argued that the primary cognitive deficit in SLI was with the structure of underlying phonological representations, which leads to a secondary limitation in the storage of novel phonological information. While the debate about the exact underlying cognitive impairment in SLI continues, the key issue for the current chapter is whether similar patterns of NWR performance are seen in children with ALI. If similar (atypical) patterns and levels of performance were evident, then this would provide solid evidence that the cognitive underpinnings of language impairment in ALI were partially the same as those underlying SLI. In this instance, we could be more confident that the similarities in language impairment in ALI and SLI were not merely a case of phenomimicry.

In fact, evidence is mounting that the neuro-cognitive underpinnings of language impairment in ALI are not the same as the neuro-cognitive underpinnings of language impairment in SLI. Children with ALI show impaired NWR relative to similar aged peers, whereas children with ASD who have unimpaired structural language do not show diminished NWR (e.g., Kjelgaard & Tager-Flusberg, 2001) This finding was taken initially as supporting the notion the "ALI = ASD + SLI" model. However, several studies have reported patterns of NWR performance among children with ALI that do not resemble those seen in SLI. Studies by Whitehouse, Barry, and Bishop (2008), and Riches et al. (2010) found a significantly greater effect of stimulus length (i.e., increasing number of syllables in a nonsense word) in SLI than in ALI, which both studies attributed to a primary problem with short-term memory in SLI, but not ALI. Such qualitative differences in NWR performance between the groups led Riches et al. (p.10) to the same conclusion as Whitehouse et al., that "the claim for a phenotypic overlap between SLI and ALI may have been overstated". More recently, Williams, Payne, and Marshall (under review) confirmed that NWR was impaired among

children with ALI relative to typical age-matched peers. However, their performance was remarkably similar in terms of levels and patterns of performance to typically developing children who were matched for *verbal mental age*, suggesting that NWR is only delayed in ALI, whereas it is deviant in SLI. Both ALI and VMA-matched typcial groups were affected in an equivalent way by the length of the stimuli, as well as by the structure of the stimuli (i.e., the position in the nonsense word of a consonant cluster). In contrast, participants with SLI (who were matched with ALI participants for age, language abilities – including profile of language impairment – and non-verbal intelligence) showed unique patterns of performance, as well as patterns of error, and performed significantly less well than all other groups.

Similar to the findings regarding NWR, children with ALI and SLI also appear to show qualitatively different patterns of performance on tests of tense marking (for a review, see Williams et al., 2008). Together, these findings present convincing evidence that the underlying neurocognitive cause of language impairment in ALI is not the same as that in SLI. Next, we consider whether ALI and SLI could be comorbid at the etiological level.

Genetics

In our view, when researchers and clinicians suggest that two disorders are comorbid, they are probably implying that surface level similarities between two disorders reflect overlapping etiology. There are several types of data that are relevant to this issue. Firstly, family studies can establish the familial aggregation of each disorder. Secondly, twin studies can be used to establish the heritability of each disorder. In this regard, the data with respect to ASD and SLI are clear; ASD runs in families (e.g., Jorde et al., 1990) and is highly

heritable (e.g., Bailey et al., 1995). Likewise, SLI runs in families (e.g., Conti-Ramsden, Falcaro, Simkin, & Pickles, 2007) and is highly heritable (e.g., Bishop, North, & Donlan, 1995; Barry, Yasin, & Bishop, 2007).

However, the critical issue to consider here is not just whether ASD and SLI are themselves familial and heritable, but also whether any covariance in features between the two disorders is familial/heritable. If two disorders, X and Y, are etiologically related, then there should be increased incidence of disorder Y among the relatives of individuals with a diagnosis of X, and vice versa. With respect to ALI and SLI, again the family data is clear; family studies of language impairment in ASD have consistently failed to find evidence suggesting that structural language impairment is familial/heritable in this disorder, unlike in SLI (e.g., Lindgren, Folstein, Tomblin, & Tager-Flusberg, 2009; for review see Williams et al., 2008). Of central importance, are the findings that the NWR deficit characteristically observed in SLI is highly familial in this disorder (e.g., Barry, Yasin, & Bishop, 2007), but show no signs of familial aggregation in ALI (Bishop et al., 2004; Lindgren et al., 2009).

To our knowledge, only one study has explored the distribution of ASD features and formal diagnoses of ASD among the families of individuals with SLI (Tomblin, Hafeman, & O'Brien, 2003). Compared to comparison families of typically developing children, Tomblin et al. found the families of children with SLI were not a) significantly more likely to contain a member with an ASD diagnosis[2], or b) show elevated ASD features. Thus, family studies provide no support for the notion that ALI and SLI are comorbid at the etiological level.

In order to establish the heritability (as opposed to familiality) of any apparent comorbidity between two disorders, a twin design can be used in which a so-called "cross-twin cross-trait"

analysis is conducted. The basic logic of the twin method can be extended using this analysis to explore the heritability of *covariance* between two traits (bivariate heritability) by comparing the score of one member of a twin pair (the proband) on trait A (e.g., ASD features) with the score of the other member of the pair (the co-twin) on trait B (e.g., language ability). Bivariate heritability provides an estimate of the extent to which variation in trait A and variation in trait B have common genetic causes. In turn, univariate and bivariate heritability values can be used to derive a genetic correlation between the two traits. Using a variant of this technique, Dworzynski, Ronald, Hayiou-Thomas, McEwan, Happé et al. (2008) found little evidence in support of the notion that ASD and SLI are genetically comorbid. From a large population-based twin sample (the Twins Early Development Study), Dworzynski et al. selected probands who achieved a score on an ASD screening measure that indicated a significant risk of ASD, and explored the (parent-reported) language abilities of their co-twins. The genetic correlation between the core social features of ASD and language abilities was negligible (r_g = .12). The genetic correlation between repetitive and restricted behaviours, and language abilities was even smaller (r_g = .10). Finally, the genetic correlation between language abilities and the final ASD feature, communication difficulties, was larger than the above correlations, but still modest (r_g = .36). Moreover, this latter correlation could have been artificially inflated, given that several of the items on the communication subscale of the ASD screening measure employed by Dworzynski et al. concerned structural language abilities, rather than necessarily communicative abilities (e.g., "Does s/he sometimes say 'you' or s/he' when s/he means 'I'?"; Does s/he sometimes lose the listener because of not explaining what s/he is talking about?").

In short, family and twin studies suggest strongly that ASD and SLI are not overlapping disorders, and that language impairment in ASD is merely a phenomimic of SLI. However,

the data from molecular genetic studies muddies the water somewhat. Several chromosomal regions have been identified as containing candidate genes for susceptibility to SLI, including 16q, 19q, and 7q (SLI Consortium, 2002, 2004). Numerous chromosomal regions have been implicated in ASD, although potential overlap with SLI is seen reliably at only one site. This site, on chromosome 7q, contains a gene (CNTNAP2) that codes for neurexin, a protein that binds neurons at the synapse in the brain. Certain, not uncommon, variations in the DNA sequence of CNTNAP2 are associated with a small but reliable decrease in language abilities among the typical population (e.g., Whitehouse, Bishop, Ang, Pennell, & Fisher, in press). Furthermore, polymorphisms of CNTNAP2 have been implicated in SLI and, in particular, in the NWR deficits that are a cognitive marker of the disorder Vernes, Newbury, Abrahams, Winchester, Nicod et al., 2008). One key concept to bear in mind here is that SLI is unlikely to result from a mutation of a single gene that has a large detrimental effect on language ability. Rather, SLI is probably the consequence of inheriting particular variants of several genes, each of which alone has only a small effect on language ability, but when inherited in combination result (through additive and/or interactive effects) in a clinically significant language disorder. Thus, a particular variant of CNTNAP2 is likely to contribute to SLI, but will be only one part of a complex causal chain.

Now, of critical importance to the debate about comorbidity of ALI and SLI, polymorphisms of CNTNAP2 have also been implicated in ASD (Arking, Cutler, Brune, Teslovich, West et al., 2008), and the association is seen most clearly among samples of language-impaired individuals with ASD (i.e., ALI; Alarcon, Abrahams, Stone, Duvall, Perederiy et al., 2008). This creates a confusing scenario, in which variation in a gene could contribute to language disorder in ALI, as well as in SLI, but (on the basis of family studies) appear heritable in the latter disorder only. Bishop (2010) offers a potential solution to this puzzle in terms of

interactions between genes. The scenario she paints is this: Imagine there are 5 genes involved in SLI (genes 1, 2, 3, 4, & 5) and 5 genes involved in ASD (genes 6, 7, 8, 9, & 10). Now imagine that gene 1 is pleiotropic, meaning that it influences multiple phenotypic traits (in this case both ASD features and language). Imagine further that a risk variant of pleiotropic gene 1 has its (negative) effect on language abilities magnified when it occurs in the presence of certain combinations of ASD risk genes (e.g., genes 6 & 7, or genes 9 & 10, but no other combinations). In this case, gene 1 would be "epistatic", meaning that its expression has been modified by other genes. In the scenario presented by Bishop, a first-degree relative of an individual with ALI could carry certain risk variants for ASD (e.g., genes 8 and 10), which result in some sub-clinical features of ASD (the broad autism phenotype). The relative could also carry the risk variant for language impairment (gene 1), but this would not be expressed in the absence of the specific *combination* of ASD risk variants. Thus, language impairment would not appear heritable in ASD, despite having a genetic basis (and, indeed, a genetic basis that also contributes to SLI). In a computational model constructed by Bishop, this scenario produced results that parallel (relatively closely, although not exactly) real-world data on prevalence and severity of language impairment, as well as its familial transmission, in ALI and SLI.

Bishop's (2010) model supports the notion that ALI and SLI share partially overlapping etiology, which lends weight to calls to consider the two disorders comorbid. Bishop is admirably cautious in reminding the reader that "the fact a simulation can fit a pattern in the observed data does not mean that the model is correct. Phenomimicry could also be involved" (p.626). However, if we assume for a moment that the model is correct, does this really support the theoretical position that ALI = ASD + SLI? According to Bishop's model, language impairment in ASD arises from the inheritance of one genetic risk variant for SLI

(of many risk variants that contribute to SLI), which has its phenotypic effects magnified by the presence of ASD risk variants that play no role in pure SLI. Thus, in Bishop's model, four (out of five) genes that contribute to SLI do *not* contribute to ALI. Furthermore, the single gene that does contribute to both disorders has a different consequence in SLI than in ALI (because of specific epistatic effects in ALI). We elaborate on this discussion in the conclusion below, but for now turn our attention to a case of comorbidity between two disorders that, in our view, more clearly merits the term.

The Case of ADHD and Dyslexia: A more Likely Example of True comorbidity?

Despite the fact that ADHD and dyslexia each affect only around 3-5% of the population, some 20-40% of individuals with a diagnosis of either disorder also manifest clinically significant signs of the other disorder (e.g., Willcutt & Pennington, 2000). In particular, dyslexia and the inattentive subtype of ADHD are thought to be more clearly comorbid than dyslexia and the hyperactive-impulsive ADHD subtype. Are these signs phenomimics or evidence of genuine underlying comorbidity?

Neuro-cognitive underpinnings

Many researchers believe that dyslexia involves a core cognitive deficit in phonological decoding (i.e., translating printed words into appropriate sounds). Although some researchers have argued for a multiple deficit account of dyslexia (e.g., Pennington, 2006), many researchers agree that an underlying deficit in phonological decoding/phonological awareness is the most proximal cognitive cause of dyslexia. As discussed above, many executive dysfunction as the core underlying neuro-cognitive cause of ADHD. The key issue with

respect to comorbidity between the two disorders concerns whether similar patterns of neuro-cognitive dysfunction are common to both disorders.

One early study by Pennington, Grossier, and Welsh (1993) provided support for the notion that ADHD in children with dyslexia was merely phenomimicry. They assessed children with pure ADHD, children with pure dyslexia, and a "comorbid" group (who had clinically significant features of both disorders) on a battery of executive functioning tasks and a battery of phonological processing tasks. Children with ADHD performed poorly on the former, but not the latter. Vice versa, children with pure dyslexia showed impaired phonological skills, but undiminished executive functioning. Crucially, the performance of the comorbid group paralleled that of the dyslexia group, but not that of the ADHD group. This suggested that the ADHD features in the comorbid group had a different underlying cognitive cause to the ADHD features in the pure form of the disorder, implying phenomimicry. Since the publication of Pennington et al.'s study, however, several studies have failed to support the phenomimic hypothesis. Rather, these studies have found that children with dyslexia who also have ADHD features perform poorly on measures of executive functioning, as well as on measures of phonological awareness (e.g., Willcutt et al., 2001).

More importantly, a meta-analysis of neurocognitive studies of ADHD and dyslexia suggested that deficits in processing speed might represent a shared neurocognitive deficit in ADHD and dyslexia (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008). Recently, McGrath, Pennington, Shanahan, Santerre-Lemmon, Barnard et al. (2011) supported this in a large-scale study involving 614 typically developing children/adolescents, and children/adolescents with ADHD/dyslexia. Participants were tested using a large battery of tasks, including

measures of phonological awareness, verbal working memory, inhibition, naming speed, and processing speed. Structural equation modelling indicated that inhibition was uniquely related to measures of ADHD (both inattention and hyperactivity-impulsivity) and phonological awareness was uniquely related to measures of dyslexia (single word reading). Critically, however, processing speed was significantly associated with measures of reading, inattention, and hyperactivity-impulsivity even after all other variables were accounted for. Associations between processing speed, and reading and inattention were larger than with hyperactivity-impulsivity, supporting the notion that the inattentive subtype of ADHD may be more likely comorbid with dyslexia. This provides solid evidence in support of the notion that ADHD and dyslexia are linked at a level deeper than mere behaviour, and that they may have partially overlapping neurocognitive causes.

The crucial point here is that comorbidity between dyslexia and ADHD (at the neurocognitive level) is not suggested merely because children with features of both disorders perform poorly on measures of executive functioning and phonological awareness. As Morton (2004) highlights, performance on a test is merely a behaviour, not a sign of underlying cognition in itself. Rather, neurocognitive comorbidity is suggested because children with a primary diagnosis of dyslexia who also have ADHD features show a very similar *profile* of performance on executive functioning and phonological processing tasks to children with pure ADHD. This similarity in profile suggests that the underlying neurocognitive system is "damaged" in a similar way in comorbid cases as it is in pure cases, and that this damage contributes to the behavioural deficits in both kinds of case. Indeed, evidence for such an overlap is strengthened by findings from studies of the genetics of ADHD and dyslexia.

Genetics

As is the case with ASD and SLI, both ADHD and dyslexia run in families and are heritable. The heritability estimate for ADHD is approximately .76 (see Faraone et al., 2005), and approximately .50 for dyslexia (e.g., DeFries, Fulker, & LaBuda, 1987), although the heritability estimate for dyslexia is higher among the most severe cases of the disorder (Bishop, 2001). As with the cases of ASD and SLI discussed above, the critical issue to consider here is not just whether ADHD and dyslexia are themselves familial and heritable, but also whether any covariance in phenotypic features between the two disorders has a common genetic basis. Several studies have suggested that it does.

Friedman, Chhabildas, Budhiraja, Willcutt, and Pennington (2003) compared rates of ADHD in children of parents who had a history of (pure) reading impairment (i.e., reading difficulties in the absence of any ADHD features) to the rates of ADHD in the children of control parents who had no history of reading difficulties. They found that significantly more families with a reading disabled parent contained a child with ADHD (35%) than did control families in which parents had no history of ADHD or dyslexia (15%). As such, ADHD appears to run in the families of people with dyslexia. However, it is important to Friedman et al. found weaker evidence of the opposite pattern of familial aggregation, namely that of dyslexia running in families containing a parent with ADHD. Over half (51%) of families containing a parent with pure ADHD contained a reading disabled child. Although a smaller percentage (39%) of control families contained a child with reading difficulties, the between-group difference was non-significant. Thus, although it is clear from these results that ADHD aggregates in the families of people with reading difficulties, it is not as obvious that reading difficulties aggregate in the families of people with ADHD. Twin studies provide

more robust evidence that genetic influences on ADHD and dyslexia are bidirectional, however.

As part of the Colorado Learning Disabilities Research Centre Twin Study, Willcutt, Pennington, Olson, and DeFries (2007) assessed the genetic correlations between reading ability and ADHD features. Probands met criteria for either ADHD or dyslexia (and some probands met criteria for both). Co-twin scores on measures of reading ability and ADHD features were then investigated. Willcutt et al. found a substantial genetic correlation between (objectively assessed) reading ability and (parent- & teacher-assessed) ADHD features. The correlation between reading ability and inattention (r_g = .72) was much larger than between reading and hyperactivity-impulsivity (r_g = .40), underscoring the close neuro-cognitive link between the inattentive ADHD subtype and dyslexia.

Willcutt et al.'s (2007) findings were closely replicated by Paloyelis, Rijsdijk, Wood, Asherson, and Kuntsi (2010) who employed a different sample (from the Twins Early Development Study), and different measures of ADHD and reading ability to Willcutt et al. Paloyelis et al. found a large genetic correlation between (parent-reported) reading difficulties and (parent-reported) inattention (r_g = .60). This correlation was more than double the size of that observed between reading difficulties and hyperactivity-impulsivity, again supporting the hypothesised link between the inattentive ADHD subtype and dyslexia.

Arguably the most convincing evidence that ADHD and dyslexia share etiological causes, rather than being phenomimics of one another, comes from a recent study by Willcutt et al. (2010). Again employing a sample of twins from the Colorado Learning Disabilities Research Centre Twin Study, Willcutt et al. extended their previous investigations of the

etiology of behavioural similarities between the two disorders by exploring potential shared genetic influences on neuro-cognition. Participants had completed a large battery of cognitive tasks, assessing cognitive domains such as working memory, processing speed, inhibition, and phonological awareness (phenotypic analysis of these variables was conducted by McGrath et al., 2011; see above). Using a specific type of structural equation modelling (a genetic Cholesky decomposition analysis), Willcutt et al. found that a single genetic factor accounted for significant covariance between processing speed, reading ability, inattention, and hyperactivity-impulsivity. Indeed, after controlling for the shared genetic influences with processing speed, there was no additional significant genetic influence on either reading ability or ADHD features. This suggests that apparent comorbidity between ADHD and dyslexia is due to shared genetic influences that lead to diminished processing speed in each disorder. Furthermore, recent studies have suggested a specific molecular genetic link between the two disorders.

As with most molecular genetic studies of developmental disorders, linkage studies of both ADHD and dyslexia have implicated a large number of chromosomal regions as harbouring susceptibility genes, with few results replicated (for reviews of the genetics of ADHD, see Faraone et al., 2005; for reviews of the genetics of dyslexia, see Paracchini, Scerri, &Monaco, 2007). However, the most replicated region of linkage to dyslexia is on chromosome 6p (e.g., Cardon, Smith, Fulker, Kimberling, Pennington et al., 1994). This region (and, indeed, polymorphism of a specific gene on 6p22) has been implicated in dyslexia in independent samples (Cope et al., 2005; Harold et al., 2006; Rice et al., 2009). Critically, this region has also been implicated in ADHD in independent studies (Wilcutt et al., 2002; Couto, Gomez, Wigg, Ickowicz, Pathare et al., 2009). In the study by Willcutt et al., this site showed strong linkage to both dyslexia phenotypes and ADHD phenotypes,

independently. This suggests that a gene in this region has pleiotropic effects, contributing to both ADHD and reading disorders. Furthermore, two other regions, on chromosomes 14q and 20q, have been identified as harbouring genes that are potentially pleiotropic for both ADHD and dyslexia phenotypes (Gayan, Willcutt, Fisher, Francks, Cardon et al., 2005). What remains important for future research to assess is whether variations in the genes at these loci are associated with processing speed in ADHD and dyslexia. Potentially, however, we have a complete causal model to account for the comorbidity between the two disorders, with specific pleiotropic genes contributing to diminished processing speed, which in turn contributes to the behavioural phenotype of both ADHD and dyslexia.

Conclusion

We discussed some of the difficulties in diagnoses developmental disorders. Disorders such as ADHD and ASD present particular diagnostic challenges not only because there are no genetic tests but because there are currently no objective cognitive tests. When discussing comorbidity between disorders we considered at what level(s) of explanation disorders need to overlap in order for them to be considered comorbid, and what evidence can be used to establish such comorbidity (or lack thereof). We highlighted that, for many, the ultimate source of comorbidity is at the etiological level. We suspect that in the coming years, molecular genetic studies will reveal many "generalist genes" that contribute to multiple disorders will emerge in the coming years (e.g., Butcher, Kennedy, & Plomin, 2006). CNTNAP2, discussed above with respect to ASD and SLI, possibly represents one such generalist gene. Indeed, given that CNTNAP2 is involved in the formation of synapses, it seems distinctly possible that it will be implicated in learning disorders other than ASD and SLI. Ultimately, however, our concern is whether our understanding of each disorder is best

served by focussing on "comorbidity" at this level of analysis. To understand developmental disorders (and have realistic hope of remediating them), we require an understanding of the causal chain between genes and behaviour, via neurobiology and cognition. Now, what appears clear from the studies cited above is that even if ALI and SLI, for instance, share partial etiological causes, the effects on neuro-cognition (and, indeed, behaviour) are quite different in each disorder. For example, in SLI, polymorphisms of CNTNAP2 are quite possibly linked to specific "damage" to the neuro-cognitive system that underpins NWR. However, as discussed above, it appears that the neuro-cognitive cause of NWR *impairment* in SLI is largely distinct from the underlying neuro-cognitive cause of NWR *delay* in ALI. Thus, even if there turns out to be a reliable overlap in the etiology of ALI and SLI, the causal pathway to behaviour is almost certain to be different in each disorder. Therefore, in our view, to talk of language impairment in ASD *being SLI* is misleading. This is not to say that genetic studies cannot inform psychology and vice versa (see Bishop, 2006 for a compelling argument in favour of "developmental cognitive genetics"), or that the discovery of generalist genes is not important. Our point is that, we must not ignore the critical differences between the disorders in the expression (at neuro-cognitive and behavioural levels) of that etiology. More important, if such generalist genes are discovered then focusing on comorbidity (rather than difference) between disorders may be more appropriate in some cases than others. For example, attempts to one wanted to remediate language impairment in ALI and in SLI, it would be counterintuitive to focus efforts on supporting the same neuro-cognitive system in each case, given that all the evidence points to different causal pathways in each disorder. On the other hand, treatment of ADHD with methylphenidate (MPH) not only remediates the core features of ADHD (see Wilens & Spencer, 2000), but also possibly improves reading ability (and basic phonological decoding skills) among children with ADHD and dyslexia features (e.g., Bental & Tirosh, 2008; Keulers, Hendriksen, Feron, Wassenberg, Wuisman-

Frerker et al., 2007). Indeed, treatment with MPH may increase activity in neural networks associated with executive/attentional functioning (Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004). Perhaps, therefore, only when "comorbid" disorders share similar causal pathways will a focus on comorbidity lead to successful remediation of both disorders.

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Notes

[1]Mainly because of space constraints, we will focus in this chapter on cognition and genetics, rather than neurobiology (but see Williams et al., 2008).

[2]Cases of ASD in the families of individuals with SLI were significantly higher than the population estimate, however. Nonetheless, this could easily be a sampling artefact, considering only a very small number of ASD cases were discovered (n = 3). Indeed, the point of employing a comparison group is, presumably, to control for the possibility of such an artefact. Therefore, the fact that the two groups of families did not differ in rates of ASD is the most important result.