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Different neurodevelopmental symptoms have a common genetic etiology

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Background: Although neurodevelopmental disorders are demarcated as discrete entities in the Diagnostic Statistical Manual of mental disorders, empirical evidence indicates that there is a high degree of overlap among them. The first aim of this investigation was to explore if a single general factor could account for the large degree of observed overlap among neurodevelopmental problems, and explore whether this potential factor was primarily genetic or environmental in origin. The second aim was to explore whether there was systematic covariation, either genetic or environmental, over and above that contributed by the potential general factor, unique to each syndrome. **Method:** Parents of all Swedish 9- and 12-year-old twin pairs born between 1992 and 2002 were targeted for interview regarding problems typical of autism spectrum disorders, ADHD and other neurodevelopmental conditions (response rate: 80 percent). Structural equation modeling was conducted on 6,595 pairs to examine the genetic and environmental structure of 53 neurodevelopmental problems. **Results:** One general genetic factor accounted for a large proportion of the phenotypic covariation among the 53 symptoms. Three specific genetic subfactors identified 'impulsivity,' 'learning problems,' and 'tics and autism,' respectively. Three unique environment factors identified 'autism,' 'hyperactivity and impulsivity,' and 'inattention and learning problems,' respectively. **Conclusion:** One general genetic factor was responsible for the wide-spread phenotypic overlap among all neurodevelopmental symptoms, highlighting the importance of addressing broad patient needs rather than specific diagnoses. The unique genetic factors may help guide diagnostic nomenclature, whereas the unique environmental factors may highlight that neurodevelopmental symptoms are responsive to change at the individual level and may provide clues into different mechanisms and treatments. Future research would benefit from assessing the general factor separately from specific factors to better understand observed overlap among neurodevelopmental problems. **Keywords:** Neurodevelopmental problems, general factor, twin study, heritability, factor analysis.

Introduction

Although delineated as separate entities in the Diagnostic Statistical Manual of mental disorders (DSM-IV; American Psychiatric Association, 2000), there is growing agreement that meeting criteria for one neurodevelopmental disorder markedly increases the risk of meeting full or subthreshold criteria for another, related disorder (Gillberg, 2010; Lee & Ousley, 2006; Simonoff et al., 2008). This diagnostic overlap is not limited to cross-sectional findings, but also occurs over time in that receiving one neurodevelopmental diagnosis predicts receiving other related diagnoses later on (Chawarska, Klin, Paul, & Volkmar, 2009; Miniascalco, Nygren, Hagberg, Kadesjö, & Gillberg, 2006). The etiology behind this extensive comorbidity is not yet well understood, but evidence indicates that there may be a broad genetic liability underlying the increased probability of expression of multiple diagnoses (Lahey, van Hulle, Singh, Waldman, & Rathouz, 2011; Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010). The aim of the current project was to identify such a genetic liability, as well as exploring the possible existence of unique syndromes, genetic or environmental, unrelated to a general factor.

Neurodevelopmental disorders

Neurodevelopmental disorders include attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASDs), tic disorders (TDs), developmental coordination disorder (DCD), and learning disorders (LDs). These are considered to constitute a related cluster of disorders because they tend to emerge before adolescence (American Psychiatric Association, 2000), remain relatively stable across adulthood (Knorring & Hägglöf, 1993), and are more frequent in boys than girls (Baird et al., 2006). Epidemiological studies have shown that they afflict several percent of the population (American Psychiatric Association, 2000; Baird et al., 2006; Fombonne, 2003; Kessler et al., 2006; Kurlan et al., 2002; Landerl & Moll, 2010). These disorders will be subsumed under the same umbrella in the DSM-5, and the term Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) has been suggested to cover the whole group (Gillberg, 2010) to draw attention to the symptomatic, genetic, neuropsychological, neurophysiological, and developmental overlap among

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these, according to the DSM-IV (American Psychiatric Association, 2000), conceptually discrete disorders.

Having a diagnosis of one of the disorders subsumed under the ESSENCE framework markedly increases the probability of being afflicted with another neurodevelopmental diagnosis (Gillberg, 2010; Lee & Ousley, 2006; Simonoff et al., 2008), indicating that they share common, underlying liabilities. Furthermore, some of the causes of these underlying liabilities appear to be familial; having a relative afflicted with a diagnosis not only increases the risk of being diagnosed with the same disorder but also with other related diagnoses (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008).

Genetic comorbidity

Multiple studies have suggested that this familial liability is primarily genetic. For example, several population-based studies have demonstrated genetic overlap between traits related to ADHD and autistic-like traits (Lundström et al., 2011; Ronald et al., 2008). This genetic relation emerges as early as 2 years of age (Ronald, Edelson, Ahserson, & Saudino, 2010) and persists into early adulthood (Reiersen, Constantino, Grimmer, Martin, & Todd, 2008). Among a sample of child and adolescent twin pairs, ADHD and DCD were partially genetically mediated (Martin, Piek, & Hay, 2006). In, perhaps, the largest study to date on this topic, Lichtenstein and colleagues (Lichtenstein et al., 2010) noted broad genetic overlap between ASDs and several other neurodevelopmental disorders. Taken together, such extensive genetic overlap among various forms of neurodevelopmental diagnoses hints toward the potential presence of a broad and general genetic liability factor.

However, it is possible that such a genetic general factor might simply represent a psychometric artifact attributable to an arbitrarily delineated diagnostic nomenclature that artificially increases overlap among constructs. That is, the observed overlap among diagnoses may be due to artificial separation of diagnoses that actually share an underlying etiology. Building a model based on overlap among symptoms (rather than diagnoses) would circumvent this potential problem (cf., Wright et al., 2013).

The goals of the current investigation were to (a) investigate whether a general liability factor influenced all neurodevelopmental symptoms, and (b) identify the potential existence of unique syndromes unrelated to a general factor. Specifically, we aimed to answer two primary sets of questions:

1 Is there a general factor underlying neurodevelopmental symptoms? If so, is it primarily genetic or environmental in origin? What does this factor measure?
2 Is there systematic covariation, either genetic or environmental, over and above that contributed by the potential general factor, unique to each syndrome?

Method

Sample

The Child and Adolescent Twin Study (CATSS; Anckarsäter et al., 2011) is a nation-wide cohort study targeting all Swedish twins at ages 9 and 12, and has ethical approval from the Karolinska Institute Ethical Review Board. The study began on 1 July 2004, and currently (31 December 2012) includes 21,450 individuals. In the CATSS, an interview company contacted twin parents by telephone and administered standardized questions covering their children's mental and physical health, as well as their social environment. The response rate was about 80 percent. In more than 85% of the sample, parent interviews were conducted with the twins' mothers; no significant differences have been found between mother and father ratings. Opposite-sex twins, twins with missing values on their cotwin, and individuals with known brain damage, chromosomal syndrome, or epilepsy were excluded. The final sample analyzed in this study consisted of 2,906 MZ pairs and 3,689 (same sex) DZ pairs.

Zygosity was determined by a panel of 48 single nucleotide polymorphisms (Hannelius et al., 2007). For twins without DNA samples or before results from molecular genetic assessments were available, an algorithm based on five questions of twin similarity derived from 571 pairs of twins with known zygosity was used. Only twins with more than 95% probability of being correctly classified were assigned zygosity by this method.

Instrument

Twin parents were interviewed according to the Autism – Tics, AD/HD, and other Comorbidities inventory (A-TAC; Hansson et al., 2005), which was developed specifically for the twin study. The purpose of the instrument was to assess a broad array of neurodevelopmental symptoms while, to facilitate epidemiological research, being relatively easy to administer. Although the symptoms can be combined to create diagnostic categories according to the DSM-IV, we treated them as dimensional markers. It consists of 96 items and includes three response options, 'no,', 'yes, to some extent,' and 'yes.' We focused on those 53 items (Table 1) that are considered to tap into core neurodevelopmental symptom areas, including 'motor control,' 'perception,' 'concentration and inattention,' 'impulsiveness and hyperactivity,' 'learning,' 'planning and organizing tasks,' 'memory,' 'language,' 'social interaction,' 'flexibility,' and 'tics.' The A-TAC

Table 1 Genetic and unique environment exploratory factor analysis

		Genetic factors				Unique environment factors		
Item	Scale	General	Impulsivity	Learning problems	Tics & autism	Autism	Hyperactivity & impulsivity	Inattention & learning problems
Often fail to pay close attention to details or make careless mistakes in schoolwork, or other activities	Inattention	**0.54**	0.26	0.23	−0.04	−0.01	0.18	**0.50**
Often have difficulty sustaining attention in tasks or play activities	Inattention	**0.58**	0.23	0.29	−0.02	0.20	**0.31**	**0.50**
Often seem not to listen when spoken to directly	Inattention	**0.60**	**0.34**	0.09	0.02	0.16	0.21	**0.41**
Difficulty following instructions and finishing tasks	Inattention	**0.60**	0.16	**0.37**	0.03	0.26	0.19	**0.46**
Often have difficulty organizing tasks and activities	Inattention	**0.66**	0.18	**0.33**	0.10	0.23	0.14	**0.45**
Often avoid tasks that require sustained mental effort (such as homework)	Inattention	**0.56**	0.20	0.27	0.03	0.17	0.12	**0.45**
Often lose things	Inattention	**0.54**	**0.40**	−0.01	−0.03	−0.12	−0.01	**0.56**
Easily distracted or disturbed	Inattention	**0.60**	**0.31**	0.19	−0.01	0.21	0.21	**0.44**
Often forgetful in daily activities	Inattention	**0.56**	**0.37**	0.04	−0.02	−0.08	−0.03	**0.58**
Difficulties keeping his/her hands and feet still or can he/she not stay seated	Hyperact-impuls	**0.56**	0.28	0.02	0.12	0.00	**0.52**	0.17
Get up and move about in class or in other situations when he/she is supposed to remain seated	Hyperact-impuls	**0.58**	0.30	0.10	0.05	0.13	**0.51**	0.16
Often run around or climb excessively compared with peers	Hyperact-impuls	**0.52**	0.26	0.03	0.10	0.01	**0.56**	0.08
Have difficulty playing calmly and quietly	Hyperact-impuls	**0.65**	0.30	0.10	0.10	0.04	**0.50**	0.08
Often act as though he/she had 'ants in his/her pants', i.e., being unable to stay still	Hyperact-impuls	**0.60**	**0.35**	0.04	0.05	−0.06	**0.57**	0.07
Talk constantly	Hyperact-impuls	**0.48**	**0.37**	−0.08	0.00	−0.07	**0.33**	−0.05
Often blurt out answers to questions before they are completed	Hyperact-impuls	**0.51**	**0.44**	−0.10	−0.04	0.00	**0.35**	−0.05
Difficulty waiting for his/her turn	Hyperact-impuls	**0.59**	**0.42**	−0.04	0.00	0.17	**0.44**	0.02
Often interrupt, or intrude on, others	Hyperact-impuls	**0.60**	**0.43**	−0.03	0.00	0.11	**0.37**	−0.02
Easily get bored	Hyperact-impuls	**0.58**	**0.40**	0.06	−0.04	0.05	0.27	0.11
Had more difficulties than expected acquiring reading skills	Learning	**0.47**	−0.03	**0.66**	−0.05	0.12	0.07	0.20
Learning is slow and laborious	Learning	**0.60**	0.11	**0.48**	0.02	0.21	−0.04	**0.31**
Have difficulties with basic maths	Learning	**0.48**	0.02	**0.57**	−0.04	0.13	−0.03	0.26
Difficulty shifting plan or strategy when this is required	Plan & org	**0.61**	**0.31**	0.06	0.08	**0.53**	0.03	0.10

(continued)

Table 1 (continued)

		Genetic factors				Unique environment factors		
Item	Scale	General	Impulsivity	Learning problems	Tics & autism	Autism	Hyperactivity & impulsivity	Inattention & learning problems
Difficulty keeping things in order	Plan & org	**0.55**	**0.36**	0.02	0.01	−0.03	0.05	**0.41**
Difficulties remembering where he/she put things	Memory	**0.55**	**0.39**	0.01	−0.03	−0.10	−0.09	**0.49**
Difficulties remembering long or multiple-step instructions	Memory	**0.66**	0.22	**0.34**	0.04	0.17	0.02	**0.41**
Difficulties learning rhymes, songs, multiplication tables, etc. by heart	Memory	**0.57**	0.03	**0.57**	0.02	0.10	0.00	0.24
Problems coordinating movements smoothly	Motor control	**0.49**	0.00	0.24	0.24	0.24	−0.08	0.17
Seem disturbed by height differences such as in connection with climbing stairs etc.	Perception	**0.38**	0.03	0.09	0.23	0.22	−0.16	0.14
Difficulty judging distance or size	Perception	**0.61**	0.10	0.23	0.22	0.24	−0.06	0.19
Oversensitive to touch or tight clothing	Perception	**0.45**	0.14	−0.02	0.23	**0.31**	−0.03	0.06
Particularly sensitive to certain sounds/noise	Perception	**0.48**	0.04	0.07	**0.31**	**0.32**	−0.02	0.10
Particularly sensitive to certain flavors, smells, or consistencies	Perception	**0.43**	0.17	−0.04	0.19	0.19	−0.11	0.04
Language development was delayed or he/she does not speak at all	Language	**0.46**	−0.09	**0.38**	0.21	0.08	0.00	−0.03
Difficulties sustaining a conversation	Language	**0.64**	0.00	**0.31**	**0.33**	**0.34**	0.01	0.14
Likes to repeat words and expressions or uses words in a way that other people find strange	Language	**0.59**	0.07	0.18	0.28	0.29	0.11	0.04
Difficulties with games of make-believe or imitates others considerably less than other children	Language	**0.54**	0.07	0.13	0.28	0.27	0.05	0.00
Talk in too high a pitch or too quietly	Language	**0.45**	0.18	0.04	0.13	0.09	0.04	−0.05
Difficulties keeping 'on track' when telling other people something	Language	**0.59**	0.18	0.26	0.08	0.22	0.06	0.22
Difficulties expressing emotions and reactions with facial gestures, prosody, or body language	Social interaction	**0.64**	0.01	0.23	**0.37**	**0.36**	−0.01	0.06
Exhibit considerable difficulties interacting with peers	Social interaction	**0.62**	0.10	0.14	**0.31**	**0.45**	0.13	0.08
Uninterested in sharing joy, interests, and activities with others	Social interaction	**0.65**	0.07	0.17	**0.34**	**0.34**	0.01	0.04
Can only be with other people on his/her terms	Social interaction	**0.54**	0.19	0.02	0.22	**0.43**	0.17	0.02
Difficulties behaving as expected by peers	Social interaction	**0.63**	0.21	0.11	0.20	**0.46**	0.26	0.13

(continued)

Table 1 (continued)

Item	Scale	Genetic factors				Unique environment factors		
		General	Impulsivity	Learning problems	Tics & autism	Autism	Hyperactivity & impulsivity	Inattention & learning problems
Other people easily influence him/her	Social interaction	**0.55**	**0.33**	0.07	0.00	0.03	0.11	0.15
Gets absorbed by interests in such a way as being repetitive or too intense	Flexibility	**0.64**	0.25	−0.01	0.24	0.29	0.00	0.04
Gets absorbed by routines in such a way as to produce problems for him/herself or others	Flexibility	**0.62**	0.18	0.01	0.30	**0.46**	−0.04	0.01
Ever engaged in strange hand movements or toe-walking when he/she was happy or upset	Flexibility	**0.49**	−0.02	0.02	**0.43**	0.16	0.12	0.06
Get obsessed with details	Flexibility	**0.60**	**0.34**	−0.06	0.14	**0.40**	−0.01	−0.04
Dislike changes in daily routines	Flexibility	**0.54**	0.28	0.00	0.11	**0.51**	−0.04	−0.01
During any period of life made involuntary sounds such as throat clearing, sneezing, swallowing, barking, or shouting	Tics	**0.33**	0.00	−0.16	**0.42**	0.13	0.14	0.19
Has made involuntary facial grimaces or body movements during any period of life	Tics	**0.33**	−0.03	−0.14	**0.43**	0.09	0.09	0.16
Make a lot of noise, for example, whistle, hum, mumble	Tics	**0.50**	0.19	−0.10	0.27	0.04	0.23	0.10

Loadings greater than |.30| are bolded. Hyperact-impuls, Hyperactivity–impulsivity. Plan & org, Planning & organization.

inventory has good internal (Hansson et al., 2005) and external validity (Larson et al., 2010).

Statistical analyses

Multivariate twin analyses examine the relative contributions of additive genetics (A), shared environment, that is, environmental variables that make twin pairs similar (C), and unique environment, that is, environmental variables that make twin pairs different (E) on the phenotypic *covariation* among variables. Greater overlap among MZs relative to DZs suggests that the phenotypic covariation is primarily driven by shared genes (A). Similarity within pairs, regardless of zygosity, suggests that the phenotypic covariation is primarily driven by shared environment (C), such as socioeconomic status, parenting styles. Dissimilarity within MZ pairs indicates that the phenotypic covariation is driven by unique environmental experiences, including, for example, separate friend groups.

To determine how many factors to extract, we examined scree plots (Cattell, 1966) and conducted parallel analyses (Horn, 1965; Raiche, 2010) based on the 53 × 53 A, C, and E covariance matrices. These matrices were derived by conducting a Cholesky decomposition of the polychoric correlation matrix (which circumvents problems of nonnormally distributed items) in Mplus (Muthén & Muthén, 1998-2010) using the unweighted least square mean and variance estimator based on a full weight matrix. Briefly, the scree plot examines the Eigenvalues (i.e., variance accounted for) based on each component and a subjective 'elbow,' that is, a sharp difference between Eigenvalues, serves as a reference point for how many nonrandom factors exist in the data. Parallel analysis compares the correlation matrix based on the observed data to a correlation matrix based on random (i.e., uncorrelated) data with the same number of parameters (i.e., same number of items and observations). The rationale is to use the structure based on the random correlation matrix as a lower baseline for the number of factors to extract from the observed data.

Subsequently, we conducted a factor analysis of the 53 symptoms to examine their latent structure. Factor analysis has shown promise in identifying latent factors across both child (Lahey et al., 2004)

and adult psychopathology (Krueger, Caspi, Moffitt, & Silva, 1998). We opted to use exploratory, rather than confirmatory, factor analysis because (a) we had no preconceived notions about its structure, (b) conducting several CFAs before settling on a final structure is, in essence, more exploratory than onfirmatory (Nesselroade & Baltes, 1984), and (c) we presumed that symptoms would cross-load, that is, we did not expect the data to have simple structure (Thurstone, 1947). We allowed the A and E factors to be different (i.e., we fit a so-called independent pathway model) because we wanted to explore whether the etiology of a potential general factor was genetic or environmental. The exploratory factor analyses (EFA; Asparouhov & Muthen, 2009) were carried out on the polychoric correlations in Mplus (Muthén & Muthén, 1998-2010) using the unweighted least square mean and variance estimator based on a full weight matrix. The factors were rotated to simple structure in the software R (R Development Core Team, 2012) using the GPArotation package (Bernaards & Jennrich, 2005).

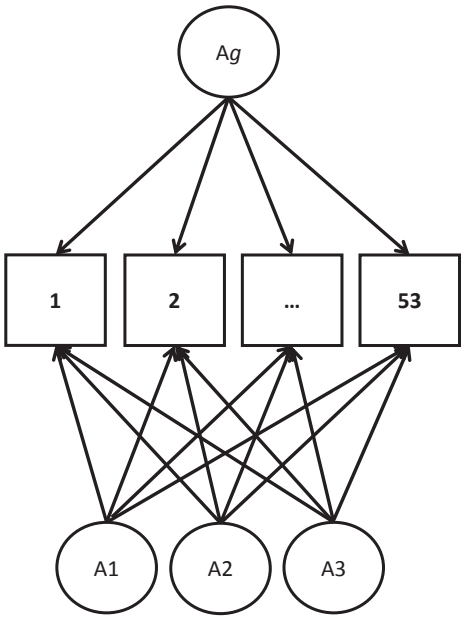

Figure 1 Hierarchical factor solution (Schmid-Leimann transformation) based on genetic factors. Ag represents the general genetic factor, whereas A1, A2, and A3 represent the three specific genetic factors

Results

Exploratory analyses

In the genetic covariance matrix, both the scree plot (Cattell, 1966) and parallel analysis (Horn, 1965) indicated the presence of three nonrandom factors. The first genetic Eigenvalue accounted for the majority of the genetic covariance, indicating the presence of a general factor. The shared environment components accounted for only a minor fraction of the total variance. In the unique environment matrix, both the scree plot and parallel analysis indicated the presence of three nonrandom factors. The unique environment did not appear to be dominated by a general factor.

Based on this information, we opted to fit a model with three genetic factors and three unique environmental factors. This model fits very well (Root Mean Square Error of Approximation, RMSEA = .01, 90% CI = .01–.01; Confirmatory Fit Index, CFI = .98; χ^2 = 13489.17, *df* = 10924). We did not extract a C factor because it only accounted for a minor fraction of the total variance.

Genetic factors

The three genetic factors were rotated to simple structure using the oblique Geomin algorithm, generating factor intercorrelations at .54, .62, and .50, which indicates the influence of a general factor. Ignoring to model a general factor may artificially increase overlap among otherwise independent phenomena, and create a potentially misleading picture of overlap among risk factors (Tellegen et al., 2003). Therefore, we proceeded to isolate the variance that could be attributed to the general factor onto a separate, isolated dimension by conducting a Schmid-Leiman (Schmid & Leiman, 1957) transformation. This involves allowing the factors to correlate, extracting a higher order factor based on the factor intercorrelations, and then regressing this higher order factor directly onto the items (Figure 1). The (three) original factors are thereby set to be orthogonal (unrelated) to the general factor, and can be interpreted as more narrow and specific subfactors. In other words, responses to items are modeled to be caused by a broad general factor as well as unique and specific subfactors that are independent of the general factor.

Following the Schmid-Leiman (1957) rotation, the general genetic factor (Table 1) accounted for 31 percent of the phenotypic variance and all items loaded positively on it (mean loading = .55, *SD* = .08, range = .33–.66). Items with large loadings tapped memory (e.g., *difficulties remembering long or multiple-step instructions*, loading = .66), autistic symptomatology (e.g., *uninterested in sharing joy, interests, and activities with others*, loading = .65), and AD/HD symptomatology (e.g., *have difficulty playing calmly and quietly*, loading = .65). Items with smaller, but still meaningful, loadings tapped language problems (*talk in too high a pitch or too quietly*, loading = .45), perception (e.g., *particularly sensitive to certain flavors, smells, or consistencies*, loading = .43), and tics (e.g., *has made involuntary facial grimaces or body movements during any period of life*, loading = .33). We interpreted this general factor as indicative of overall severity (cf., Hopwood et al., 2011), but without the ability to discriminate between different types of symptoms.

The first genetic subfactor, transformed to be unrelated to the general factor, accounted for six percent of the phenotypic variance and included items such as *often interrupt, or intrude on, others* (loading = .43), *difficulties remembering where he/she put things* (loading = .39), *often blurt out answers to questions before they are completed* (loading = .44), and *talk constantly* (loading = .37). We interpreted this subfactor as impulsivity. It is important to note, however, that this factor included not only pure impulsivity items but also items designed to measure different problem areas (e.g., memory, planning, and flexibility), underscoring the value of analyzing symptoms rather than diagnoses.

The second genetic subfactor accounted for five percent of the phenotypic variance and included items such as *had more difficulties than expected acquiring reading skills* (loading = .66), *difficulties learning rhymes, songs, multiplication tables, by heart* (loading = .57), *difficulty following instructions and finishing tasks* (loading = .37), and *often have difficulty organizing tasks and activities* (loading = .33). We interpreted this subfactor as learning problems.

The third genetic subfactor, accounting for four percent of the phenotypic variance, included items such as *during any period of life made involuntary sounds such as throat clearing, sneezing, swallowing, barking, or shouting* (loading = .42), *ever engaged in strange hand movements or toe-walking when he/she was happy or upset* (loading = .43), *difficulties expressing emotions and reactions with facial gestures, prosody, or body language* (loading = .37), and *uninterested in sharing joy, interests, and activities with others* (loading = .34). We interpreted this subfactor as a blend between tics and autism.

Unique environment factors

The three unique environment factors were largely unrelated (correlating .14, .29, and .20 following oblique rotation), indicating that they were not dominated by a general factor. Subsequently, to ease interpretation, we rotated the solution to orthogonal simple structure with Varimax. The first unique environment factor (Table 1), accounting for six percent of the phenotypic variance, included items such as *exhibit considerable difficulties interacting with peers* (loading = .45), *difficulty shifting plan or strategy when this is required* (loading = .53), *dislike changes in daily routines* (loading = .51), and *gets absorbed by routines in such a way as to produce problems for him/herself or others* (loading = .46). We interpreted this unique environmental factor as autism.

The second unique environment factor, accounting for five percent of the phenotypic variance, included items such as *often act as though he/she had 'ants in his/her pants', i.e., being unable to stay still* (loading = .57), *difficulties keeping his/her hands and feet still or cannot stay seated* (loading = .52), *difficulty waiting for his/her turn* (loading = .44), and *often interrupt, or intrude on, others* (loading = .37). We interpreted this unique environment factor as a blend of hyperactivity and impulsivity.

The third unique environmental factor, accounting for six percent of the phenotypic variance, included items such as *often forgetful in daily activities* (loading = .58), *often has difficulty sustaining attention in tasks or play activities* (loading = .50), *often fails to pay close attention to details or make careless mistakes in schoolwork, or other activities* (loading = .50), and *difficulties remembering long or multiple-step instructions* (loading = .41). We interpreted this unique environmental factor as inattention and learning problems.

Discussion

Our results showed that a broad general genetic factor influenced all 53 neurodevelopmental symptoms. This is in accord with previous research noting that neurodevelopmental diagnoses tend to co-occur (Gillberg, 2010; Lee & Ousley, 2006; Simonoff et al., 2008) and that the overlap is largely genetic in origin (Lichtenstein et al., 2010; Ronald et al., 2008). In addition, although much smaller in magnitude compared with the general factor, we also isolated specific genetic and environmental factors. These loadings tended to concur with the designated scale modules, but there were also meaningful differences, underscoring the value of analyzing specific problems rather than scales or diagnoses.

The general genetic factor

The model identified the influence of a strong genetic general factor tapping a broad liability to suffer from a wide range of nonspecific symptoms. Furthermore, we ruled out that this general factor was a psychometric artifact based on current diagnostic nomenclature because our analyses were based on the overlap among *symptoms*. This suggests that the same genes that influence symptom one also influences symptom two, even if they tap into clinically different problem areas. That is, it appears that the vast majority of genes rendering individuals susceptible for neurodevelopmental disorders are 'generalists' (Kendler, Heath, Nichols, Martin, & Eaves, 1987; Kovas & Plomin, 2007). One speculation is that the co-occurrence among neurodevelopmental symptoms arises due to impaired development of the brain during critical stages in gestation, infancy, or early childhood. This, in turn, could lead to problems that would affect the normal growth process in areas such as learning, social interaction, and behavioral control. The greater similarity among monozygotic compared with dizygotic twins implies that this impaired process is primarily genetic in origin.

The identification of a general genetic factor has two potential implications. First, molecular attempts

to find genes related to specific conditions or disorders may be problematic; given that genes appear to predispose individuals to a wide range of neurodevelopmental symptoms, it seems unlikely that one or a few set of genes would influence one disorder, but not others. Second, the general factor would seem to provide a strong argument against systems that appear to advocate a 'splitter' rather than 'lumper' approach to diagnosis. When children display problems in one area, it might be more important to, as early as possible, set up a strategy for helping with all related symptoms rather than trying to help only with a specific diagnosis (which often will change over time). In other words, it may be more beneficial to focus on treating the underlying general factor, rather than whatever specific diagnosis it might manifest as at any given time (Gillberg, 2010).

Specific genetic factors

Aside from the general genetic factor, we also isolated three specific genetic factors that highlighted the uniqueness of syndromes. Although much smaller in magnitude compared with the general factor, these three specific genetic factors were interpreted as 'impulsivity,' 'learning problems,' and 'tics and autism,' respectively. These factors differed somewhat compared with the related disorders in the DSM-IV (American Psychiatric Association, 2000), and may inform future diagnostic nomenclature. For example, compared with the DSM-IV, the genetic impulsivity factor consisted not only of pure impulsivity/hyperactivity items but also of problems with memory, planning, and flexibility. Furthermore, the observed covariation among inattention items was primarily due to the unique environment, indicating only a weaker genetic basis for the AD/HD inattention diagnostic subcategory. One speculation is that learning problems, a seemingly genetically influenced syndrome, may decrease motivation and thereby attentiveness toward academic tasks for some but not all twins within a pair, such that inattentive covariation becomes attributed to the unique environment.

Unique environment factors

The unique environment factors differed from the genetic factors in two respects. First, they were not dominated by a general factor, and, second, they appeared easier to interpret with greater correspondence to the designated scale modules. With regard to the absence of a general factor, this implies that the unique environment may serve to 'guide' symptomatology in a given direction, given the presence of genetically influenced psychopathology in the first case. In other words, whereas 'generalist genes' may predispose individuals to a wide array of problems, environmental forces may drive the manifestation of a specific syndrome (Kendler et al., 1987; Kovas & Plomin, 2007).

With regard to the relative ease of interpretation of the unique environment factors, it is possible that the clarity of these factors represents some kind of rating bias, such that parents had a schematic representation of what various forms of neurodevelopmental syndromes 'ought to' look like, and attributed one set of symptoms to one twin over the other in a manner consistent with this schema (Shweder, 1975). On the other hand, to the extent that the unique environment factors actually represent a true effect, and not a rating bias, they might highlight that part of the phenotypic covariation among neurodevelopmental symptoms is responsive to manipulation and change at the individual level (Turkheimer, 2011). Furthermore, the structural differences between the genetic and nonshared environment may provide clues into differential mechanisms and, following, differential treatments.

Limitations and future directions

First, all observations were based on a single source of report. Although one would expect parents to know their children well, teachers, peers, and the participants themselves may have had access to information that the parents did not. Furthermore, clinical interviews conducted by experts may have generated a more detailed assessment of the problem area. Second, we only examined the relation among items. It remains unknown what variables might lead to the development of the genetic and environmental factors, and what kind of problems these factors might lead to as the children enter adolescence and, later on, adulthood.

Conclusion

Why is there such pronounced overlap among neurodevelopmental symptoms? This investigation demonstrated the importance of a general genetic factor as the primary contributor to this extensive overlap. Apart from the general factor, we also identified specific factors, of both genetic and environmental origins, that differentiated among types of syndromes. The unique genetic factors may prove to have diagnostic value, whereas the unique environmental factors may indicate the potential for intervention in the observed syndromes. We would like to underscore the importance of measuring general and specific factors separately to further the etiological understanding of neurodevelopmental problems.

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Key points

- The large degree of phenotypic overlap among neurodevelopmental problems is primarily due to one general factor.
- This general factor is genetic in origin.
- Aside from the general factor, there is systematic variation, both genetic and environmental, that appear to drive manifestation of specific syndromes.
- The field of neurodevelopmental psychopathology may benefit from increasing its focus on the general factor.

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