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Individual differences in anatomy predict reading and oral language impairments in children

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Developmental dyslexia (DD) and specific language impairment (SLI) are disorders of language that differ in diagnostic criteria and outcome. DD is defined by isolated reading deficits. SLI is defined by poor receptive and expressive oral language skills. Reading deficits, although prevalent, are not necessary for the diagnosis of SLI. An enduring question is whether these two disorders are qualitatively different or simply differ quantitatively along a dimension of severity. Here we address this problem by examining neuroanatomical correlates of reading and language in children with learning disabilities. We asked whether a quantitative anatomical risk index derived from previous work could predict behavioural profiles in a heterogeneous sample of 14 boys and 8 girls (11–16 years of age) with reading and language impairments. The results confirmed our predictions that (i) children with relatively smaller and symmetrical brain structures (negative risk indices) would have the severe comprehension impairments typical of SLI; (ii) children with larger, asymmetrical brain structures (positive risk indices) would have poor word reading in the presence of relatively preserved comprehension, a profile typical of DD; and (iii) the best performance would be seen in children with anatomical risk indices near zero (normal anatomy). Also, in confirmation of previous work, rapid automatic naming was not predicted by the anatomical risk index, but by anatomical measures derived from the frontal lobes. These results highlight the key significance of comprehension deficits in distinguishing DD from SLI. Reading impaired children with and without comprehension deficits appear to occupy neuroanatomical domains on the opposite sides of normal.

Keywords: reading disability; asymmetry; brain anatomy; child; planum temporale

Abbreviations: DD = developmental dyslexia; RAN = rapid automatic naming; SLI = specific language impairment

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Introduction

Developmental dyslexia (DD) and specific language impairment (SLI) are disorders of language that differ in diagnostic criteria and outcome. SLI is defined by poor expressive and receptive oral language. Although reading impairment is not one of the criteria, 50% of SLI children go on to develop difficulties with reading (Catts *et al.*, 2002). DD, on the other hand is diagnosed by a 'pure' reading impairment, usually detected on non-word or single word reading. This word reading impairment is attributed to deficient phonological awareness of the sound units in the alphabetic principle that translates written into spoken words (Lyon *et al.*, 2003). The resultant lack of print exposure impedes comprehension and vocabulary growth, thereby depriving overall language development. Although substantial progress has been made in identifying functional pathways that are anomalous in DD (Eden and Zeffiro, 1998; Berninger and Richards, 2002; Eden and Moats, 2002; Demonet *et al.*, 2004), there is no consensus on the relationship between disorders of spoken and written language and their underlying pathophysiology (Berninger, 2006).

Oral and written languages in DD

Traditional evaluations of reading disabilities include measures of reading (non-word and single word reading, reading comprehension and reading speed) and reading related processes such as phonological awareness and rapid automatic naming (RAN). Substantial research (Denckla and Rudel, 1976; Wolf and Bowers, 1999) has demonstrated that dyslexic children are frequently impaired in RAN, a skill that requires the rapid naming of blocks of letters, numbers, colours, or objects and may depend on frontal circuits for working memory and executive function (Thompson-Schill *et al.*, 2002; Misra *et al.*, 2004).

It has been suggested that DD is associated with depressed reading comprehension compared with listening comprehension (Pennington, 1999; Shapiro, 2001), but assessment of oral language skills is not standard practice in research studies or clinical evaluations of DD. In the few cases when oral language has been addressed, investigators have found that many children with reading disability also meet criteria for SLI (McArthur *et al.*, 2000; Catts *et al.*, 2002).

Some studies demonstrate that even for those dyslexic children who do not meet the formal diagnosis of SLI, speech perception ability can be impaired (Manis *et al.*, 1996; Breier *et al.*, 2002) and other oral language skills vary widely. However, individuals with DD also demonstrate heterogeneous behavioural profiles in other domains, making it difficult to determine the specificity of these varied observations (Leonard *et al.*, 2001; Amitay *et al.*, 2002; Leach *et al.*, 2003; Ramus *et al.*, 2003).

The prevalence of oral language impairments in DD has led some theorists to propose that DD and SLI simply differ quantitatively along a dimension of severity (Tallal *et al.*, 1993). Additional support is provided by genetic data indicating that reading impairments occur within families of SLI probands (Flax *et al.*, 2003). Bishop and Snowling (2004) have introduced a somewhat different view, however. They propose a two-dimensional model where non-phonological and phonological deficits vary independently. Children with impairments limited to the phonological domain would have DD while children with deficits in both phonological and non-phonological domains would be diagnosed with SLI. The group with impairments restricted to the non-phonological domains is labelled 'poor comprehenders'. Some previous anatomical findings accord with the idea that comprehension and phonological deficits have different origins. For example, we found that brain measures in reading impaired students with poor comprehension skills more closely resembled those of children with SLI than those of students with DD (Leonard *et al.*, 2002; Eckert *et al.*, 2003).

The neuroanatomy of reading and language impairment

Surprisingly little attention has been directed to possible distinctions between the neuroanatomical substrates of SLI and DD. To our knowledge, there have been no neurobiological studies comparing these two groups or examining their neuroanatomical characteristics in the context of comprehensive behavioural evaluations. Instead, each diagnostic category has been studied in isolation. In DD Galaburda *et al.* (1985) described the first biological evidence as enlarged right plana temporale leading to atypical symmetry. This investigation was post-mortem and thus included individuals with a wide variety of deficits including some in oral language. More recent studies of DD [reviewed in Eckert and Leonard (2003); Shapleske *et al.* (1999)] have not found planar symmetry, but have described a bewildering range of anatomical differences between children with DD and controls. These differences include reductions in temporal lobe, frontal lobe, caudate, thalamus and cerebellum (Brown *et al.*, 2001), insula, anterior superior neocortex (Pennington *et al.*, 1999), occipital cortex (Eckert *et al.*, 2005), relative increases in the size of temporal and parietal plana (Green *et al.*, 1999) and posterior cortex (Pennington *et al.*, 1999). There also may be subtle alterations in callosal morphology (Robichon and Habib, 1998; von Plessen *et al.*, 2002), inferior frontal gyrus and cerebellum (Eckert *et al.*, 2003). Two studies using diffusion weighted imaging have described a localized loss of directionality either bilaterally or restricted to the left hemisphere, possibly due to alterations in pathway location (Klingberg *et al.*, 2000; Deutsch *et al.*, 2005).

The findings in SLI have been more consistent. Starting with the pioneering work of Jernigan *et al.* (1990) several studies have reported a decrease in size of left hemisphere language structures (Gauger *et al.*, 1997), generally reduced brain size (Preis *et al.*, 1998), or reversal of normal leftward asymmetry (Plante *et al.*, 1991; Jackson and Plante, 1996; Herbert *et al.*, 2005) There are exceptions, however. Preis *et al.* (1998) reported no differences in planar asymmetry in a group of well matched children with and without oral language impairments while Herbert *et al.* (2003) found enlarged rather than reduced brain size in children with oral language impairments. In a later study the enlargement in brain size was attributed to a specific increase in intrahemispheric fibre pathways (Herbert *et al.*, 2004).

Relationships between anatomy and behavioural measures in DD and SLI

Anatomical differences between groups with a diagnosis of SLI or DD and normal controls are not always robust across samples. One obvious source for these differences is variability in the diagnostic inclusion and exclusion criteria. One approach to this anatomical and behavioural variability within a diagnostic category is to investigate consistencies in the relation between neuroanatomy and behavioural variation across or within samples of both controls and individuals with impairments. For example, in a study that used the Steinmetz system of Sylvian fissure classification (Steinmetz *et al.*, 1990), typical (type 1) Sylvian fissure

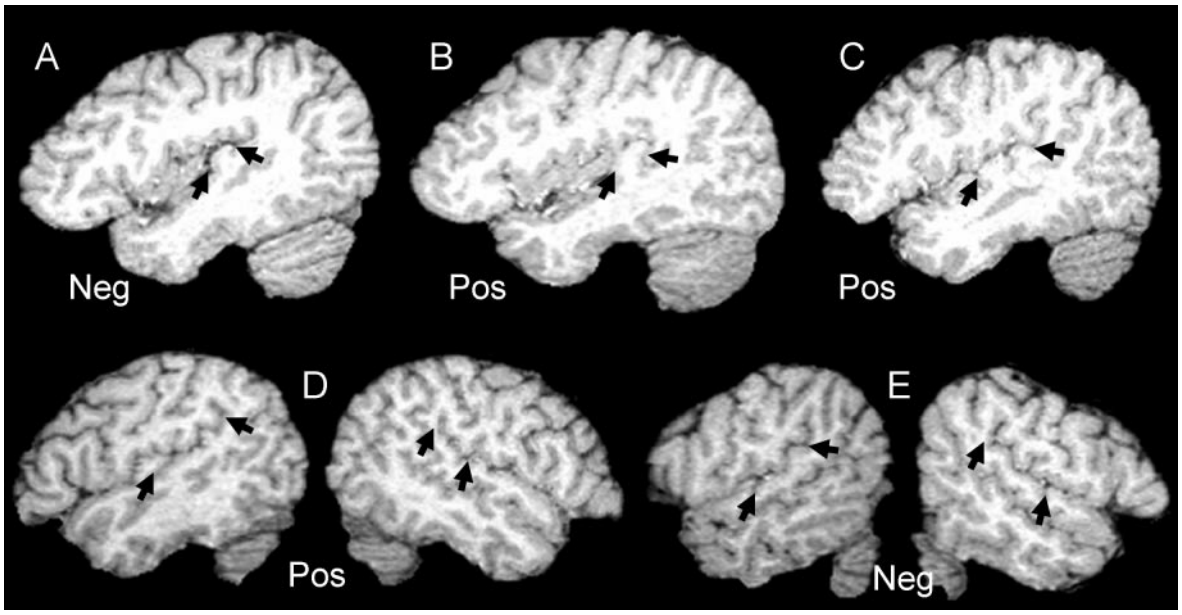

Fig. 1 MRI images of Heschl's gyrus (*top*) and the planum temporale (*bottom*). (**A**) Small Heschl's gyrus typical in brains with negative anatomical risk indices (Neg); (**B**) Large Heschl's gyrus typical of brains with positive anatomical risk indices (Pos). (**C**) Duplicated Heschl's gyri typical of brains with positive anatomical risk indices. (**D**) Typical leftward asymmetry of the planum temporale. (**E**) A large planum temporale in the right hemisphere.

morphology in the left hemisphere predicted better performance on a variety of linguistic and cognitive measures across both dyslexic and control children (Hiemenz and Hynd, 2000).

It has also been reported that planar asymmetry predicts a number of cognitive abilities including verbal IQ (Rumsey *et al.*, 1997), reading ability (Eckert *et al.*, 2001) and measures of functional lateralization, including dichotic listening (Hugdahl *et al.*, 2003) and lexical decision (Chiarello *et al.*, 2004). Recently, we found that the size of pars triangularis in the inferior frontal gyrus predicted RAN in a sample of children with DD (Eckert *et al.*, 2003). Another study of high functioning adult dyslexics and controls identified four anatomical measures (rightward cerebral asymmetry, summed leftward planar and parietal asymmetry, the size of an anomalous second Heschl's gyrus on the left and rightward cerebellar anterior lobe asymmetry) that were *negatively* associated with non-word reading but not with RAN or reading comprehension (Leonard *et al.*, 2001). These associations between continuous measures of anatomical and behavioural variation suggest that categorical diagnoses may obscure variation that could be important in establishing genetic and neurobiological substrates.

To test the idea that different behavioural profiles might be associated with different anatomical profiles, a cumulative measure derived from the four anatomical measures described above was applied in a *post hoc* analysis to a sample of high functioning adults with dyslexia (Leonard *et al.*, 2001). This measure successfully distinguished nine dyslexic individuals with specific phonological impairment from three with low average reading comprehension. Consistent with Bishop and Snowling's (2004) model, individuals with these different behavioural profiles formed two clusters at the opposite ends of the control distribution of anatomy. This was the first intimation that anatomical features of individuals with different types of reading impairment might differ qualitatively, rather than quantitatively. In a subsequent study of children with SLI and/or DD, we identified three more variables (the total size of the cerebral hemispheres, the first Heschl's gyrus on the left and planum temporale asymmetry) that when combined with the four measures described above, produced an anatomical risk index that separated 25 children and adults with SLI or comprehension deficits from 23 individuals with more limited reading impairments (Leonard *et al.*, 2002).

The cluster of individuals with reading impairments had strongly positive anatomical risk indices [larger cerebral and auditory cortex (Heschl's gyri) and more marked asymmetries than the population norm]. Individuals with comprehension deficits had strongly negative anatomical risk indices (smaller cerebral and auditory cortex and less marked asymmetries than the population norm). Adult controls had normally distributed anatomical risk indices, with a mean near zero, the middle of the anatomical distribution. Examples of MRI images from brains with positive and negative anatomical risk indices are shown in Fig. 1.

The validity of this anatomical dimension was tested prospectively, in a group of 103 normal children aged 5 to 12, to (i) evaluate its relationship to measures of reading comprehension and/or word reading and (ii) examine if

anatomical/behavioural relations were stable across chronological age (Leonard *et al.*, 2002). The results showed that normal children with positive anatomical risk indices showed declines in non-word reading, but not reading comprehension, with age. Normal children with anatomical risk indices near zero showed increases on all standardized reading measures with age. In contrast to children with SLI, however, normal children with negative anatomical risk indices did not have reading and language deficits. This last finding indicates that the anatomical risk index is not a neurological marker for disability but could indicate risk factors that interact with other neurobiological and environmental factors to adjust the threshold for disability.

In a more recent study, carefully diagnosed children with DD, who had severe reading and RAN deficits in the context of above average verbal intelligence, had smaller frontal, cerebellar and occipital areas than control children (Eckert *et al.*, 2003, 2005), rather than the predicted positive anatomical risk indices. In this sample, the size of the left and right pars triangularis in the inferior frontal gyrus (Broca's area on the left) as well as the right anterior lobe of the cerebellum, predicted RAN speed. Although a majority of these children had negative anatomical risk indices, a subsequent analysis demonstrated that the anatomical risk index was not associated with RAN (C. M. Leonard, unpublished data). These findings suggested that RAN, word reading, and comprehension deficits may be associated with different neuroanatomical indicators.

The fact that some children with a classic dyslexia 'double deficit' profile (Wolf and Bowers, 1999) shared aspects of the anatomical phenotype (a negative anatomical risk index) of children with SLI, rather than that of children with isolated word reading deficits was unexpected. These results emphasized the need for further anatomical studies that examine a broad range of reading and oral language measures in order to establish reliable neuroanatomical–behavioural correlates in these domains without imposing arbitrary limits with diagnostic boundaries.

Study objectives

The present study was conducted to characterize brain–behavioural relationships in a sample of 22 children aged 11–16 who were identified by the US public school system as having reading and language impairments. We acquired brain structure measurements and examined these either individually or based on a formula combining several of these anatomical measures (the anatomical risk index) derived from the studies described above (Leonard *et al.*, 2002). We sought to confirm three predictions based on previous work: (i) a risk for multiple oral and written language deficits is associated with the negative side of the anatomical risk index distribution; (ii) a risk for word reading deficits, with comprehension relatively spared, is associated with the positive side of the distribution; (iii) RAN speed is associated with variation in frontal and cerebellar measures rather than the anatomical risk index. This third prediction was based on findings in the study of Eckert *et al.* (2003). In this study of children with DD, the surface areas of the left and right pars triangularis in Broca's area, and the right anterior cerebellar lobe volume, but not the anatomical risk index, were positively associated with faster RAN.

Support of prediction 1 [and replication of the results of study 2 in Leonard *et al.* (2002)] would be provided by demonstration of (i) positive associations between the anatomical risk index and oral language and reading comprehension measures and (ii) more widespread deficits in oral language in children with negative risk indices than children with positive risk indices. Support for prediction 2 would be provided by demonstration of a significant curvilinear contribution (inverted U shaped function) to the relationship between the anatomical risk index and word reading but not comprehension. Support for prediction 3 [and a replication of Eckert *et al.* (2003)] would be provided if RAN speed were associated with pars triangularis, cerebral volume, and right anterior cerebellar lobe size, but not the anatomical risk index.

Material and methods

Participants

The children in this reading and language impaired sample were identified by teachers in the Maryland and Virginia public schools as potential participants in an intervention study that also employed functional MRI. The imaging was conducted at Georgetown University and approved by their Institutional Review Board. Twenty-two children participating in the study had structural scans suitable for anatomical study. Of these 22, 18 had IQ scores available from school records (mean = 97 $\pm$ 19). Student IQ scores were based on extant school records of the Cognitive Abilities Test (Thorndike and Hagen, 1993) or the Wechsler Intelligence Scale for Children (Wechsler, 1991). Where no ability records were available, students were administered the Otis–Lennon School Ability Test (Otis and Lennon, 1995). Because of the multiple assessment measures, these scores were not included in the statistical analysis. The children's consent/assent was obtained according to the Declaration of Helsinki after the study purposes had been explained. They received age-appropriate gifts for their participation.

Behavioural tests

Reading related processes

The ability to conceptualize and manipulate phonemes presented aurally (phonemic awareness) was assessed by asking the child to delete phonemes from ten strings as in 'Say pan. Say it again but don't say /p/'. The ability to use phonological rules to decode meaningless letter strings presented visually was assessed with a test of phonologically regular non-words (Word Attack), from the Woodcock Johnson Psycho-Educational Battery, Revised (WJR) (Woodcock and Johnson, 1989). RAN was assessed with the Denckla and Rudel plates for colours, objects, letters and numbers (Denckla and Rudel, 1976). The average time for colour and object naming (CO) and the average time for number and letter naming (NL) were converted to standard scores based on age norms

Table 1 Demographic, reading and language scores of a group of 14 boys and 8 girls with reading impairment and structural MRI scans

Measure	Mean	SD
Age	13.0	1.4
Dextrality	0.62	0.61
Reading related processes		
Phonemic deletion	87	16
Non-word reading	82	14
RAN-NL	83	16
RAN-CO	87	16
Written language		
Real word reading	82	14
Reading comprehension	85	20
Reading rate	76	21
Spelling	80	16
Oral language		
Receptive language	82	19
Expressive language	81	20

Performance is expressed in terms of standard scores. Assessment measures are described in Material and methods.

derived from an epidemiological sample (L. Flowers, personal communication).

Written language proficiency

Reading accuracy for single real words was assessed with the WJR Word Identification subtest and reading comprehension was assessed with the WJR Passage Comprehension subtest, a cloze procedure requiring children to supply a missing word based on context (four children did not receive this test). Reading rate was measured with the Gray Oral Reading Test (Wiederholt and Bryant, 1992) and spelling was measured with the spelling subtest of the Wide Range Achievement Test (Wilkinson, 1993).

Oral language

Oral language was assessed with the receptive and expressive subscales from the Clinical Evaluation of Language Functions (Semel *et al.*, 1995).

Handedness

A quantitative measurement of dextrality (ranging from −1 to 1) was obtained using the Edinburgh Handedness Inventory. Table 1 gives means and standard deviations for the demographic and behavioural variables.

MRI acquisition and preliminary image processing

MRI data were acquired on a Siemens 1.5 T Magnetom with a T1 MPRAGE Turboflash technique. Scan parameters were TR: 10 ms; TE: 4 ms; flip angle: 10°; matrix: 256 × 128 × 128, image voxel size = 0.98 × 0.98 × 1.25 mm. After headers containing identifying characteristics had been removed and images concatenated into a series, scans were transferred to the University of Florida as approved by their Institutional Review Board, assigned random numbers and reformatted into 1 mm thick slices in the Talairach planes using scripts written in PVWave (Visual Numerics, Boulder, CO).

Overview of anatomical analysis

Measurement scripts, written in PVWave, displayed images on which cursor tracings could be made by raters blind to hemisphere of origin and subject identity. Two raters made each measurement and differences of >15% were resolved by discussion. The procedures and measures were identical to those in previous studies (Leonard *et al.*, 2001; Eckert *et al.*, 2003). The anatomical risk index was calculated following the procedure described in Leonard *et al.* (2002) adding weights for the measures indicated in italics below to a constant of −4.31. The weights and the constant were derived from the discriminant function developed in a sample of 48 reading and language impaired subjects. In previous work, the anatomical risk indices of healthy children were normally distributed around zero. Children with positive indices have (i) relatively more leftward asymmetry of the planum temporale and combined plana, and cerebellar anterior lobe; (ii) relatively more rightward asymmetry of cerebral volume, and (iii) larger values for cerebral volume and the surface areas of the first and second Heschl's gyri. Children with negative indices have (i) relatively less leftward asymmetry of the planum temporale and combined plana, and cerebellar anterior lobe; (ii) relatively more leftward asymmetry of cerebral volume; and (iii) smaller values for cerebral volume and Heschl's surface area.

Technical details

Cerebral hemispheres

The volume of each cerebral hemisphere was measured by tracing the area enclosed by the dura on every fourth sagittal image, and summing the averages of adjacent areas after multiplying by the width of the inter image gap. [Volumes calculated with this method correlate 0.98 with volumes calculated from measurements of every image and 0.96 with automatically stripped and segmented volumes (Eckert *et al.*, 2005)]. Inter-rater reliability of this measure is 0.95 (intraclass correlation). The volumes of the two hemispheres were totalled and normalized for sex (normalized cerebral volume), based on the means of normal samples of girls and boys. The coefficient of asymmetry of the cerebral hemispheres (cerebral asymmetry) was calculated by dividing the left–right difference by the left–right average. When the left hemisphere is larger, the coefficient is positive. The weight for normalized cerebral volume in the risk index formula was 0.95 (larger volumes increase the risk index in the positive direction) and for cerebral asymmetry was −13.8 (rightward asymmetry increases the risk index in the positive direction).

Anterior cerebellum

The outlines of the anterior lobes of the cerebellum were traced in sagittal images. Every 1 mm thick section on which the primary fissure could be seen was outlined, the outlined areas were multiplied by section thickness (1 mm) and added to calculate the volume in each hemisphere. As the primary fissure becomes indistinct laterally (Larsell and Jansen, 1972), the lateral boundary of the anterior lobe was defined as the image on which the superior cerebellar vessels disappeared. Inter-rater reliability for this measurement is 0.87. The coefficient of asymmetry (anterior cerebellar asymmetry) was calculated as described for the cerebral hemispheres. The weight for anterior cerebellar asymmetry in the risk index formula was 3.1 (leftward asymmetry increases the risk index in the positive direction).

Heschl's gyri

The surface areas of the primary Heschl's gyrus and, when present, a second Heschl's gyrus (*see* Fig. 1; Leonard *et al.*, 1998) were traced between their limiting sulci (horizontal arrows in Fig. 1) on consecutive sagittal images between Talairach $x = 34$ and $x = 48$ (standardized mm lateral to the midline). An index of each surface area was calculated by adding together the lengths of the tracings in successive sections multiplied by the section thickness (1 mm). Inter-rater reliabilities are 0.9 for the primary Heschl's gyrus and 0.85 for the second Heschl's gyrus. The weight in the risk index formula for the primary Heschl's gyrus was 0.7 and for the second Heschl's gyrus was 0.63 (large size increases the risk index in the positive direction).

Planum temporale and parietale

The surface area of the planum temporale was measured between the posterior boundary of either the first or the second Heschl's gyrus (if the second Heschl's gyrus was fully separated), and the termination of the horizontal branch of the Sylvian fissure. An index of the surface area was calculated by averaging the length of each tracing between Talairach $x = 46$ and $x = 56$ as reported previously (Leonard *et al.*, 1993, 1996; Foundas *et al.*, 1994). Inter-rater reliability for these measurements is 0.85. The coefficients of asymmetry (planum temporale asymmetry, planum parietale asymmetry) were calculated as described for cerebral volume. On the average, the asymmetry coefficient for the planum temporale is positive (left greater than right) and the asymmetry coefficient for the planum parietale is negative (right greater than left). Summing the coefficients of asymmetry for the planum temporale and planum parietale (summed planar asymmetries) provided an index of the mean asymmetry of the coefficients for the two banks. The weight for planum temporale asymmetry in the risk index formula was 1.27 and for the summed planar asymmetries was 0.55 (leftward asymmetry increases the risk index in the positive direction).

Pars triangularis

The surface area of pars triangularis was measured from Talairach $x = 39$ to $x = 48$ in the right hemisphere and from Talairach $x = 40$ to $x = 49$ in the left hemisphere using the method described in Foundas *et al.* (1998). Measurements were made by tracing the surface formed by the anterior ascending ramus and the anterior horizontal ramus of the Sylvian fissure. These major branches of the Sylvian fissureposit are easily identified in most brains. The surface was traced from the dorsal tip of the ascending ramus, toward the Sylvian fissure and then followed the horizontal ramus to its dorsal termination. Inter-rater reliability for these measurements is 0.85. The coefficient of asymmetry was calculated as described above. The pars triangularis is not entered into the formula for the anatomical risk index because it was not one of the measures taken in the studies that developed the index (Leonard *et al.*, 2002).

Statistical analysis

All variables were entered into spreadsheets and analysed with PC-SAS (SAS, 2002). The univariate procedure was used to assess the significance of the asymmetry quotients. Preliminary analyses using Student's t, χ^2, and correlation coefficients (Pearson r) investigated the relation between demographic, anatomical and behavioural variables. Two anatomical subtypes were formed by splitting the anatomical risk index distribution at 0. Since the numbers of children in the two subtypes were small and unequal, both non-parametric and parametric tests were run. As the results of the two types of test differed only in one case, the parametric results are reported, with the exception noted.

To provide evidence concerning prediction 1 (that a risk for multiple oral and written language deficits would be associated with the negative side of the anatomical risk index distribution), three strategies were used. (i) Correlation coefficients (Pearson r) between the behavioural measures, age and the anatomical risk index were calculated. (ii) Student's t was used to assess the significance of the group difference in each assessment measure. To avoid type 1 error, preliminary analyses were made with composite scores in each of the three domains. When these three differences proved significant ($P < 0.05$), subsequent analyses were conducted of each individual assessment score. (iii) Since there were outliers in some of the domains, deficit profiles were created by defining a deficit as a standard score of 85 or below. (Since the phoneme test was not standardized, a deficit was arbitrarily defined as a score below 8.) The number of deficits was totalled for each child and Student's t was used to assess the significance of the group difference.

To provide evidence concerning prediction 2 (that a risk for word reading deficits, with comprehension relatively spared, would be associated with the positive side of the distribution), hierarchical regression analysis was employed to determine if the quadratic component (obtained by squaring) of the anatomical risk index predicted significant variance in a word reading composite when it was entered into a model that accounted for the effects of age and the anatomical risk index. Squaring the anatomical risk index eliminates the influence of the sign (i.e. the relation strengthens when both extreme positive and extreme negative indices are associated with lower performance). A significant contribution from the quadratic component would demonstrate a significant curvilinear (inverted U shape) aspect to the relation between the anatomical risk index and word reading scores. The word reading composite was obtained by averaging non-word reading and single real word reading scores together. The same model was also used to predict a comprehension composite obtained by averaging the receptive oral language and reading comprehension scores together.

To provide evidence concerning prediction 3 (that RAN speed would be associated with variation in frontal and anterior cerebellar measures rather than the anatomical risk index), correlation coefficients were calculated to evaluate the strength of the association between RAN-NL, RAN-CO, anterior cerebellar lobes, pars triangularis and the anatomical risk index. Hierarchical multiple regression, controlling for age and brain volume, was used to identify unique contributions for each anatomical variable to the prediction of a composite (hereafter referred to as RAN) obtained by averaging RAN-NL and RAN-CO.

Results

The means and standard deviations of the anatomical measures are presented in Table 2. These values are not significantly different from those reported for the children with DD studied in Eckert *et al.* (2003). There were no significant sex differences in any measure (all t's < 1.0) although there was the expected trend for cerebral volume to be bigger in boys, $t(21) = 1.93$, $P = 0.07$. The coefficient of asymmetry of the planum temporale was strongly and significantly leftward, $t(21) = 4.95$, $P < 0.0001$, while the coefficients of

Table 2 Brain measurements in a group of 14 boys and 8 girls with reading and language impairments and structural MRI scans

Measure	Mean	SD
Volume (cc)		
Cerebrum		
Boys	1160	114
Girls	1071	83
Normalized for sex	−0.72	1.16
Surface area (cm^2)		
First Heschl's gyrus, left	3.75	1.07
Second Heschl's gyrus, left	0.81	1.03
Pars triangularis, left*	2.64	0.82
Pars triangularis, right*	2.28	0.81
Coefficient of asymmetry		
Cerebrum	−0.00	0.03
Planum temporale	0.53	0.50
Averaged planum temporale and parietale	0.06	0.67
Anterior lobe of the cerebellum	−0.00	0.10
Pars triangularis*	0.16	0.39
Anatomical risk index	−0.42	1.86

Normalization of brain volume is based on the mean of a sample of 166 children and adults.
*Values not included in anatomical risk index.

summed planar asymmetry, cerebral asymmetry, anterior cerebellar lobe, pars triangularis, and the anatomical risk index were not significantly different from zero.

There were no significant associations between any of the anatomical measures or the anatomical risk index and age (*P*'s > 0.22). There were 8 children with positive risk indices (larger, more asymmetrical brain structures) and 14 children with negative risk indices (smaller, more symmetrical brain structures). Children with positive and negative risk indices did not differ in mean age (positive: 13.1 years ± 1.9; negative: 12.9 years ± 1.2, $t < 1.0$) or sex distribution (positive: 6 boys, 2 girls; negative: 8 boys, 6 girls, $\chi^2 < 1$). The parametric test (but not the non-parametric median test) demonstrated a significant difference in dextrality (positive: 0.90 ± 0.10; negative: 0.46 ± 0.72) because all four adextral children (quotients ⩽0) had negative risk indices. The variance of the dextrality quotient was significantly different in the two subtypes, $F(13) = 45.19$, $P < 0.0001$, and the $t(14)$ with degrees of freedom adjusted for unequal variances was 2.26 ($P < 0.0001$).

Evidence concerning prediction 1: a risk for multiple oral and written language deficits is associated with the negative side of the anatomical risk index distribution

(i) Table 3 presents the zero order correlation coefficients between all the assessment measures, age and the anatomical risk index. As predicted, there was a significant correlation between both reading comprehension and oral receptive language and the anatomical risk index (both *r*'s = 0.58, $P < 0.01$). Contrary to predictions, however, word and non-word reading measures had equally strong associations with the anatomical risk index ($r = 0.60$, $r = 0.61$, $P < 0.01$), while expressive oral language was more weakly correlated ($r = 0.44$, $P < 0.05$). To explore these relations further, scatter plots of the relationship between the anatomical risk index, non-word reading, reading comprehension and the two measures of oral language are presented in Fig. 2. The four graphs look strikingly similar. Children with negative risk indices performed poorly on all tests, while the best performance was associated with anatomical risk indices slightly above 0 (normal anatomy). The few children with extremely positive risk indices showed variable deficits. The strong positive correlations between anatomy and both reading and oral language measures appear to be due to the preponderance of children with negative indices and low scores in all domains.

(ii) The reading profile analysis confirmed that children with negative anatomical risk indices had more deficits than children with positive risk indices. Figure 3 shows that the mean scores for children with positive anatomical risk indices were consistently and significantly better than those for children with negative indices. The positive subtype showed significantly better performance ($P < 0.05$) on two of the phonological measures (phoneme deletion and non-word reading), three of the written language measures (single word accuracy, passage comprehension, and reading rate) and both of the oral language measures. The effect sizes for significant differences were between 1 and 1.2. The only skills in which the two subtypes were not significantly different were spelling ($P = 0.06$), RAN-NL and RAN-CO (*P*'s > 0.3).

Table 4 demonstrates striking differences in the deficit profiles at the top and bottom of the anatomical risk index distribution. Children at the bottom of the distribution (negative risk indices) were more likely to have multiple deficits than children at the top of the distribution (positive risk indices). Children with negative indices were also more likely to have deficits in both expressive and receptive oral language. This group had a mean of 7.4 ± 2.7 deficits while children with positive indices had a mean of 2.75 ± 2.9 deficits [$t(21) = 3.76$, $P < 0.01$]. Not one child with a positive index had a deficit in either receptive language or reading comprehension.

Evidence concerning prediction 2: a risk for word reading deficits, with comprehension relatively spared, is associated with the positive side of the distribution

The hierarchical multiple regression analysis presented in Table 5 revealed that, as predicted, the quadratic component of the anatomical risk index contributed

Table 3 Zero-order correlation coefficients between the reading and language measures, age and the anatomical risk index

Measure	Non-word	Real word	Read comp	Read rate	Spell	RAN-NL	RAN-CO	Oral rec	Oral exp	Age	ARI
Phoneme	0.56**	0.42	0.37	0.39	0.31	0.36	0.28	0.53*	0.47	−0.04	0.50*
Non-word		0.80****	0.70***	0.71***	0.69***	0.60**	0.56**	0.55*	0.75****	−0.28	0.61**
Real word			0.91****	0.80****	0.87****	0.60**	0.52*	0.66***	0.70***	−0.35	0.60**
Read comp				0.66***	0.71***	0.49	0.48	0.73***	0.67***	−0.34	0.58**
Read rate					0.76****	0.60**	0.49	0.65**	0.54*	−0.37	0.54*
Spell						0.59**	0.58**	0.45	0.49	−0.58**	0.33
RAN-NL							0.78****	0.38	0.30	−0.35	0.26
RAN-CO								0.44	0.35	−0.54*	0.15
Oral rec									0.76****	−0.34	0.58**
Oral exp										−0.34	0.44*
Age											0.25

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

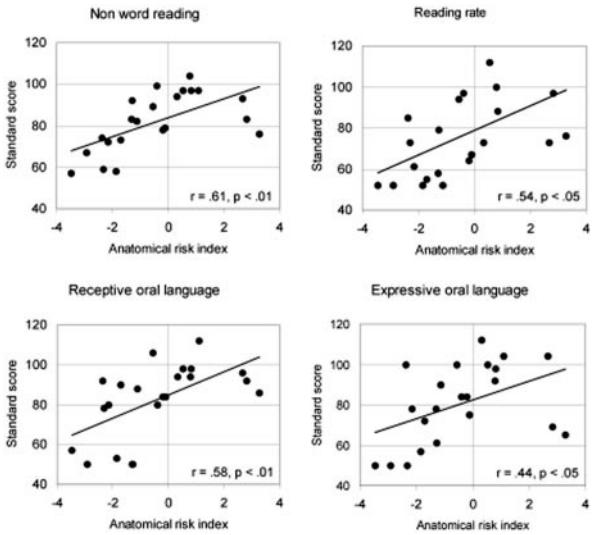

Fig. 2 Graphical demonstration of the relation between the anatomical risk index and some reading and language skills. Extremely negative anatomical risk indices are associated with poor performance on all tests. The best performance is associated with anatomical risk indices near zero.

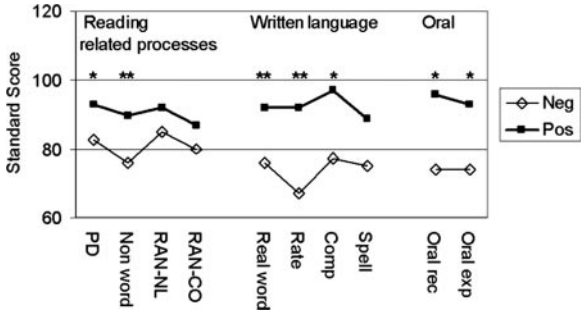

Fig. 3 Graphical comparison of the means for 14 children with negative anatomical risk indices and 8 children with positive anatomical risk indices. Children with positive risk indices perform better on all measures (*$P < 0.05$; **$P < 0.01$). Significant effect sizes ($P < 0.05$) were ⩾1.0.

significant variance to the prediction of the word reading composite (after accounting for the contributions of age and the linear component), but not the comprehension composite. The significant curvilinear (inverted U shape) relationship between the anatomical risk index and the word composite is due to the drop off in word reading scores for children with strongly positive anatomical indices.

Evidence concerning prediction 3: RAN speed is associated with variation in frontal and cerebellar measures rather than the anatomical risk index

This prediction was partially confirmed. There was a positive association between RAN and the surface area of the left pars triangularis ($r = 0.47$, $P < 0.05$), a trend towards a negative association with the surface area of the right pars triangularis ($r = -0.37$, $P < 0.09$) and a highly significant positive association with the coefficient of asymmetry ($r = 0.73$, $P < 0.0001$) (*see* Fig. 4). A positive association indicates that children with rightward asymmetry of pars triangularis had slower RAN than children with leftward asymmetry.

The association between cerebral volume and RAN showed a trend towards significance ($r = 0.42$, $P = 0.052$). There was no relationship between RAN and the cerebellar anterior lobe measures (r's < 0.15) or the anatomical risk index ($r = 0.24$, $P = 0.34$). Hierarchical multiple regression was used to determine that the left and right pars triangularis predicted unique variance in RAN after accounting for the contributions of age and cerebral volume. The model explained 73% of the variance in RAN, $F(4,17) = 15.26$, $P < 0.0001$ (*see* Table 6).

The results of Eckert *et al.* (2003) were only partially replicated. In the previous study, RAN correlated positively with left and right pars triangularis size, right anterior cerebellar and cerebral volume, while there was no correlation between RAN and the coefficient of pars triangularis asymmetry.

Table 4 Deficit profiles

Anatomical risk index	Age	Sex	PD	Non-word	Real word	Read comp	Read rate	Spell	RAN-NL	RAN-CO	Oral rec	Oral exp	Total deficits
Neg													
−3.46	13.0	f	×	×	×	×	×	×	×	×	×	×	10
−2.91	15.0	m	×	×	×	×	×	×	×	×	×	×	10
−2.4	11.9	m	×	×	×		×	×		×			6
−2.31	12.3	m	×	×	×	×	×	×	×	×	×	×	10
−2.15	12.3	f		×	×	NA	×	×	×	×	×	×	8
−1.85	14.3	m	×	×	×	×	×	×	×	×	×	×	10
−1.7	11.5	f	×	×	×		×	×				×	6
−1.3	14.4	m	×	×	×	NA	×	×	×	×	×	×	9
−1.28	12.4	m	×		×	×	×	×			×	×	7
−1.12	13.6	m		×	×	×	×	×					5
−0.55	12.1	f				NA		×		×			2
−0.4	11.3	f	×								×	×	2
−0.19	12.2	m	×	×	×	×	×	×	×	×	×	×	10
−0.1	14.4	f		×	×	×	×	×			×	×	7
Pos													
0.33	12.3	f					×	×	×	×			4
0.54	12.2	m											0
0.79	12.0	m				NA							0
0.83	11.8	f	×										1
1.1	11.1	m											0
2.68	15.6	m					×	×	×	×			6
2.83	16.2	m	×	×	×			×	×	×		×	7
3.28	14.0	m		×	×		×	×		×		×	7
Total deficits			12	13	14	8*	15	17	10	13	10	13	

Crosses indicate standard scores ⩽85. Children are listed in order of anatomical risk index.
*Scores were not available for four children.

Table 5 Hierarchical multiple regression demonstrates that the quadratic component of the anatomical risk index (ARI^2) contributes unique variance to the word reading composite after accounting for age and the linear component of the anatomical risk index

Level	Variable	R^2	ΔR^2	$P<$	Std. beta	t	$P<$
Word composite							
1	Age	0.15		0.15	−0.33	−1.57	0.15
2	Age				−0.52	−3.76	0.01
	ARI		0.55	0.0001	0.76	5.51	0.001
3	Age				−0.31	−2.23	0.05
	ARI				0.69	5.8	0.0001
	ARI^2		0.11	0.01	−0.40	−2.97	0.01
Comprehension composite							
1	Age	0.10		0.11	−0.39	−1.9	0.10
2	Age				−0.58	−4.26	0.001
	ARI		0.52	0.0001	0.74	5.49	0.001
3	Age				−0.51	−3.14	0.01
	ARI				0.72	5.16	0.0001
	ARI^2		0.01	0.41	−0.13	−0.85	0.4

The quadratic component does not contribute unique variance to the comprehension composite.

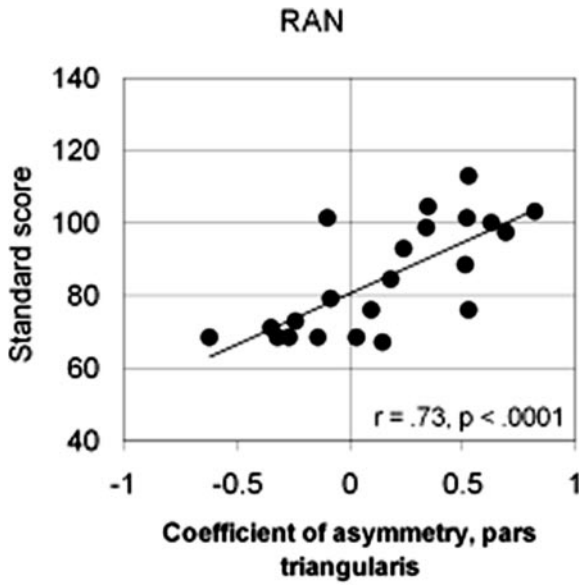

Fig. 4 The degree of leftward asymmetry in pars triangularis is associated with RAN speed. Children with rightward asymmetry (negative coefficient) have worse scores than children with strong leftward asymmetry (positive coefficient).

Discussion

This study addressed the question of whether neuroanatomical measures associated with SLI and DD differ quantitatively in degree or qualitatively in kind. In confirmation of the results reported earlier (Leonard *et al.*, 2002), we found that children at the opposite ends of an anatomical continuum had different types of reading and language deficits. Children with negative anatomical risk

Table 6 Hierarchical multiple regression demonstrates that the surface areas of the left and right pars triangularis predict unique variance in RAN after accounting for age and normalized cerebral volume

Level	Variable	R^2	ΔR^2	$P <$	Std. beta	t	$P <$
1	Age	0.23		0.05	−0.48	−2.42	0.05
2	Age				−0.55	−3.26	0.01
	Cer vol		0.24	0.01	0.50	2.97	0.01
3	Age				−0.49	−3.09	0.004
	Cer vol				0.45	2.89	0.0001
	Lptr		0.11	0.05	0.34	−2.16	0.05
4	Age				−0.38	−3.21	0.01
	Cer vol				0.40	3.43	0.01
	Lptr				0.53	4.22	0.001
	Rptr		0.22	0.001	0.49	−3.97	0.001

Cerebellar measures contributed no unique variance and were dropped from the model.

indices (smaller symmetrical brain structures) had severe deficits in all aspects of reading and language function, including comprehension (*see* Fig. 3 and Table 4). Children with positive anatomical risk indices (larger more asymmetrical brain structures) had fewer deficits, with relative sparing of receptive language and reading comprehension, a profile typical of DD. Contrary to prediction, however, oral expressive language was not spared in two children with strongly positive anatomical risk factors.

In general, the varied nature of the reading and language profiles in this group of children with reading impairment is consistent with a growing consensus that the reading and language disorders are heterogeneous and that many children may not fit neatly into diagnostic categories (Bishop and Snowling, 2004; Herbert *et al.*, 2005). The two new implications of our present results are that (i) children at both ends of the anatomical spectrum may have oral language impairments and (ii) there is a qualitative difference in the neural substrate of behavioural profiles that appear to simply differ in severity. The fact that the underlying neural substrates for children with and without comprehension deficits differ in opposite directions from normal anatomy suggests that disorders that appear to differ quantitatively may have substantially different origins.

Planum temporale asymmetry in DD

An enduring misconception is the idea that the planum temporale is symmetrical in children with DD. Even though thorough reviews of the literature have established that individuals with reading disabilities have normal or increased left–right asymmetry of the planum temporale (Eckert and Leonard, 2000, 2003; Shapleske *et al.*, 1999) planum temporale symmetry continues to be cited as a characteristic of DD (Toga and Thompson, 2003). In this study, the results confirmed that the distribution of planum temporale asymmetry in this reading impaired sample was similar to that described in the first large scale study of post-mortem brains (Geschwind and Levitsky, 1968). In that study the planum temporale was longer in the left hemisphere in 65% of the sample. In the present sample, 75% of the children had plana temporale that were longer in the left hemisphere. This finding agrees with that of Preis *et al.* (1998) but differs from that reported by De Fosse and colleagues (De Fosse *et al.*, 2004) and Herbert *et al.* (2005) in samples of children with oral language impairments. In these studies, the cortical parcellation technique used to measure the volume of grey matter in the planum temporale included the planum parietale as well. More research will be required to determine the role of differing diagnostic and measurement criteria in the production of conflicting findings.

Findings in the present sample did not confirm previous reports of an association between planum temporale asymmetry and many reading and language variables (Rumsey *et al.*, 1997; Eckert *et al.*, 2001). Our original failure to replicate brain/behaviour associations in new samples drove the development of the anatomical risk index (Leonard *et al.*, 2002). Large data sets will be required to determine the genetic, cognitive and developmental differences between samples that are associated with differences in the pattern of brain/behaviour correlations.

Is DD resolved SLI?

The differing profiles seen in children at the two ends of the anatomical distribution are somewhat reminiscent of the profiles described in the longitudinal sample identified on the basis of oral language difficulties in early childhood (Bishop and Edmundson, 1987). A series of papers by Bishop, Snowling, Stothard and colleagues have described developmental changes in the reading and language profiles of these children. At age 15, children with persistent SLI resembled children with 'general delay', the profile associated with negative risk indices. In contrast, children with SLI that had resolved by age 5, and who were normal readers at age 8 (Bishop and Adams, 1990), regressed by age 15 and showed below average phonological and literacy skills (Stothard *et al.*, 1998; Snowling *et al.*, 2001), similar to children with positive risk indices. Stothard and her colleagues pointed out that these children would not qualify for a traditional 'discrepancy' definition of DD, because their reading skills were not outside the normal range, a feature that resembles that of the children with reading impairment studied in Leonard *et al.* (2002), and the adults in other samples that did not meet traditional research criteria for DD (Leonard *et al.*, 1993, 2001; Ramus *et al.*, 2003).

Although no MRI scans are available on the children studied by Bishop, Snowling and Stothard, one might predict that the children with persistent SLI and those with resolved SLI might fall on opposite ends of the anatomical risk index continuum. The children with positive anatomical risk indices in the present study did not have large discrepancies between oral language and reading scores, a pattern resembling that of the children with resolved SLI in Stothard *et al.* (1998).

Although there was no association between age and the anatomical risk index, there was an unexpected clustering of older children at both the positive and negative ends of the continuum. Examination of Table 4 reveals that younger children (ages 11–12) tend to be clustered in the middle of the table, with anatomical risk indices close to 0, while older children tend to cluster at both negative and positive extremes. The association between age and the absolute value of the anatomical risk index was significant (Pearson $r = 0.48$, $P < 0.05$). Since such dramatic changes in cerebral size and asymmetry are unlikely to occur with maturation, it appears more likely that the clustering of age, severe deficits and high positive and negative indices arises from referral bias. The older children in this sample may have more persistent deficits that have proved resistant to treatment. Future work should investigate possible causal relations between age, deficit severity and anatomy.

One interesting difference between the children in the two anatomical subtypes was that all four left handed children had negative anatomical risk indices. We have also seen this association in a sample with schizophrenia but not in normal controls (C. M. Leonard, unpublished data). If such an association proves to be reliable, it might suggest a partial resolution of the conflicting literature on handedness and pathology (Beaton, 1997; Bishop, 2001). An elevated incidence of adextrality in the developmental disorders may be limited to individuals with certain genetic and neurobiological characteristics. Adextrality may not be a risk factor for altered cognition unless it is associated with other, yet to be determined, risk factors. If this interpretation proves correct, it might turn out that limiting the participation of adextrals in research studies reduces the generalizability of the findings to clinical populations.

One of the original motivations for the present study was the strikingly different behavioural phenotype associated with negative risk indices in study 1 of Leonard *et al.* (2002) and Eckert *et al.* (2003). In the former sample, children with negative risk indices had the multiple oral and written language deficits typical of SLI. In the latter sample, children with negative risk indices had normal oral language but severe reading spelling and RAN deficits (Berninger *et al.*, 2006). The present study has provided additional evidence for the association of oral language deficits and negative risk indices. But the characteristics of the sample reported on in Eckert *et al.* (2003) demonstrate that anatomy is not destiny. A negative anatomical risk index is not sufficient for the development of oral language deficits. There is clearly a complex interplay between genetic, environmental, educational and neurobiological factors in the development of reading and language phenotypes (Berninger *et al.*, 2001; Berninger, 2006).

The anatomy of RAN

Another implication of the present study is that the anatomical substrates for word and non-word naming, reading comprehension and reading rate differ from those for RAN. The former measures are predicted by the anatomical risk index, while RAN is predicted by frontal measures. These findings provide neurobiological support for the position that deficits in RAN and word reading are separable risk factors for DD (Wolf and Bowers, 1999) and that slow RAN speed does not simply provide additional evidence for a phonological processing deficit. The contention that these two processes contribute independent variance to reading skill is supported by other work (Compton *et al.*, 2001).

As discussed in the introduction, Wolf and Bowers (1999) showed that children who have a 'double deficit' in both phonological decoding of non-words and RAN have a particularly severe form of DD. Examination of Table 4 reveals that 7 out of 9 children with double deficits in both non-word reading and RAN had the negative anatomical risk indices previously associated with SLI. This finding, together with the prevalence of negative risk indices in the sample with double deficits reported in Eckert *et al.* (2003), suggests the surprising possibility that some anatomical measures in children with double and single deficits may differ from normal in opposite directions on the neuroanatomical index. The fact that RAN is associated with variation in the anatomy of the inferior frontal gyrus is consistent with findings of a correlation between RAN speed and brain activity during reading in typical readers (Turkeltaub *et al.*, 2003). It also is in agreement with present concepts of frontal-temporal participation in working memory. Functional imaging studies (Becker *et al.*, 1999; Collette and Van der Linden, 2002) suggest that a neural network composed of structures in the left inferior frontal gyrus (called Broca's area on the left) and parietal cortex comprise Alan Baddeley's articulatory loop (Baddeley, 1986). Thompson-Schill *et al.* (2002) recently proposed that 'the left inferior frontal gyrus subserves a general, non-mnemonic function of selecting relevant information in the face of competing alternatives'.

Strengths and weaknesses of the study

The major strength of this study was its use of an anatomical risk index that had been developed in independent samples to predict behaviour in a new sample. The sample also had a comprehensive assay of processing, literacy and oral language measures. Although the children varied widely in behavioural profile and age, and many of the children would not meet research criteria for either SLI or DD, the variation in behavioural profile could be seen as a strength, because it enabled us to test hypotheses about the shape of the relation between anatomical and behavioural variables that had not been possible in more homogeneous samples.

This study's major weaknesses are the small size of the sample relative to its heterogeneity and the absence of consistent measures of non-verbal and verbal intelligence. There were so many different behavioural profiles that some of most interesting conclusions rest on a few children at the extremes of the anatomical continuum. Since consistent

measures of intelligence were not available for the children it is not possible to determine which children would fit standard criteria for either DD or SLI. The fact that children with negative anatomical risk indices had multiple written and oral language deficits raises the possibility that these children have the general deficits associated with low IQ rather than a 'specific' language deficit. It should be pointed out, however, that none of these children had received a diagnosis of mental retardation and that each child had been identified by teachers as a candidate for reading remediation. Since an inability to use language restricts the social environment, measured IQ tends to drop in children who receive an early diagnosis of SLI (Jernigan *et al.*, 1990). These temporal changes mean that the complex links between anatomy, IQ and language skills can not be understood in the absence of longitudinal studies that include measures of the child's linguistic, social and educational environment.

Another possible weakness is the use of subjective tracing methods rather than automated segmentation and averaging to a reference template. But it is possible that the use of manual tracing may represent a strength, rather than a weakness. Recent comparisons between manual and automated methods applied to the same data sets have concluded that manual methods may be particularly sensitive to variation in structures such as the Sylvian fissure branches (Tisserand *et al.*, 2002; Eckert *et al.*, 2005). Our confidence in the tentative conclusions that have been reached using these imperfectly reliable anatomical methods is strengthened by their consistency with previous anatomical results from our own groups, the behavioural data of Bishop and her colleagues, and the theoretical approach of Wolf. Future studies are planned to determine whether the inclusion of regional grey and white matter measures strengthens the behavioural associations of the anatomical risk index.

Functional consequences of a more precise definition of the phenotype

Even if future studies show that the anatomical risk index consistently distinguishes groups of children with different prognoses it may be unreasonable to expect that anatomical information would be included as part of a diagnostic work up to help guide decisions concerning therapy. It is interesting, however, to speculate on how these anatomical variations might be related to variability in functional connectivity. Subdividing learning disabled groups by anatomy and connectivity might demonstrate deficits in different large scale functional networks (Fox *et al.*, 2005).

Questions that could be addressed in future research are (i) the importance of the various reading and oral language, measures as well as IQ, in defining anatomically homogeneous behavioural phenotypes; (ii) the role of anatomical and behavioural maturation; (iii) the role of the environment and experience in both anatomical and behavioural development; and (iv) the functional significance of these neurobehavioural relationships for educational placement, intervention and long term prognosis.

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References

Amitay S, Ahissar M, Nelken I. Auditory processing deficits in reading disabled adults. J Assoc Res Otolaryngol 2002; 3: 302–20.

Baddeley A. Working memory. New York: Oxford; 1986.

Beaton AA. The relation of planum temporale asymmetry and morphology of the corpus callosum to handedness, gender, and dyslexia: a review of the evidence. Brain Lang 1997; 60: 255–322.

Becker JT, MacAndrew DK, Fiez JA. A comment on the functional localization of the phonological storage subsystem of working memory. Brain Cogn 1999; 41: 27–38.

Berninger VW. Defining and differentiating dyslexia, dysgraphia, and language learning disability within a working memory model. In: Silliman E, Mody M, editors. Language impairment and reading disability-interactions among brain, behavior, and experience. New York: Guildford. In press.

Berninger VW, Richards TL. Brain literacy for educators and psychologists. Orlando FL: Academic Press; 2002.

Berninger VW, Abbott R, Thomson J, Raskind W. Language phenotype for reading and writing disability: a family approach. Sci Stud Read 2001; 5: 59–105.

Berninger VW, Abbott R, Thomson J, Wagner R, Swanson HL, Wijsman E, et al. Modeling developmental phonological core deficits within a working-memory architecture in children and adults with developmental dyslexia. Sci Stud Read 2006; 10: 165–98.

Bishop DVM. Individual differences in handedness and specific speech and language impairment: evidence against a genetic link. Behav Genet 2001; 31: 339–51.

Bishop DVM, Adams C. A prospective study of the relationship between specific language impairment, phonological disorders and reading retardation. J Child Psychol Psychiatry 1990; 31: 1027–50.

Bishop DVM, Edmundson A. Language-impaired four-year-olds: distinguishing transient from persistent impairment. J Speech Hear Disord 1987; 52: 156–73.

Bishop DVM, Snowling MJ. Developmental dyslexia and specific language impairment: same or different? Psychol Bull 2004; 130: 858–86.

Breier JI, Gray LC, Fletcher JM, Foorman B, Klaas P. Perception of speech and nonspeech stimuli by children with and without reading disability and attention deficit hyperactivity disorder. J Exp Child Psychol 2002; 82: 226–50.

Brown WE, Eliez S, Menon V, Rumsey JM, White CD, Reiss AL. Preliminary evidence of widespread morphological variations of the brain in dyslexia. Neurology 2001; 56: 781–3.

Catts HW, Fey ME, Tomblin JB, Zhang X. A longitudinal investigation of reading outcomes in children with language impairments. J Speech Lang Hear Res 2002; 45: 1142–57.

Chiarello C, Kacinik N, Manowitz B, Otto R, Leonard C. Cerebral asymmetries for language: evidence for structural-behavioral correlations. Neuropsychology 2004; 18: 219–31.

Collette F, Van der Linden M. Brain imaging of the central executive component of working memory. Neurosci Biobehav Rev 2002; 26: 105–25.

Compton DL, DeFries JC, Olson RK. Are RAN- and phonological awareness-deficits additive in children with reading disabilities? Dyslexia 2001; 7: 125–49.

De Fosse L, Hodge SM, Makris N, Kennedy DN, Caviness VS, Jr., McGrath L, et al. Language-association cortex asymmetry in autism and specific language impairment. Ann Neurol 2004; 56: 757–66.

Demonet JF, Taylor MJ, Chaix Y. Developmental dyslexia. Lancet 2004; 363: 1451–60.

Denckla M, Rudel R. Rapid 'automatized' naming (R.A.N.). Dyslexia differentiated from other learning disabilities. Neuropsychologia 1976; 14: 471–9.

Deutsch GK, Dougherty RF, Banner R, Siok WT, Gabrieli JDE, Wandell BA. Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. Cortex 2005; 41: 354–63.

Eckert MA, Leonard CM. Structural imaging in dyslexia; the planum temporale. Ment Retard Dev Disabil Res Rev 2000; 6: 198–206.

Eckert MA, Leonard CM. Developmental disorders: dyslexia. In: Hugdahl K, Davidson R, editors. Brain asymmetry. Cambridge MA: MIT Press; 2003.

Eckert MA, Lombardino LJ, Leonard CM. Planar asymmetry tips the phonological playground and environment raises the bar. Child Dev 2001; 72: 988–1002.

Eckert MA, Leonard CM, Richards TL, Aylward EH, Thomson J, Berninger VW. Anatomical correlates of dyslexia: frontal and cerebellar findings. Brain 2003; 126: 482–94.

Eckert M, Leonard CM, Wilke M, Eckert M, Richards T, Richards A, et al. Anatomical signatures of dyslexia in children: unique information from manual and voxel based morphometry brain measures. Cortex 2005; 41: 304–15.

Eden GF, Moats L. The role of neuroscience in the remediation of students with dyslexia. Nat Neurosci 2002; 5 (Suppl): 1080–4.

Eden G, Zeffiro T. Neural systems affected in developmental dyslexia revealed by functional neuroimaging. Neuron 1998; 21: 279–82.

Flax JF, Realpe-Bonilla T, Hirsch LS, Brzustowicz LM, Bartlett CW, Tallal P. Specific language impairment in families: evidence for co-occurrence with reading impairments. J Speech Lang Hear Res 2003; 46: 530–43.

Foundas A, Leonard CM, Gilmore R, Fennell E, Heilman KM. Planum temporale asymmetry and language dominance. Neuropsychologia 1994; 32: 1225–31.

Foundas AL, Eure KF, Luevano LF, Weinberger DR. MRI asymmetries of Broca's area: the pars triangularis and pars opercularis. Brain Lang 1998; 64: 282–96.

Fox MD, Snyder AZ, Vincent JL, Corbetta MD, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 2005; 102: 9673–8.

Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive cases with cortical anomalies. Ann Neurol 1985; 18: 222–33.

Gauger LM, Lombardino LJ, Leonard CM. Brain morphology in children with specific language impairment. J Speech Lang Hear Res 1997; 40: 1272–84.

Geschwind N, Levitsky W. Human brain: left-right asymmetries in temporal speech region. Science 1968; 161: 186–7.

Green RL, Hutsler JJ, Loftus WC, Tramo MJ, Thomas CE, Silberfarb AW, et al. The caudal infrasylvian surface in dyslexia: novel magnetic resonance imaging-based findings. Neurology 1999; 53: 974–81.

Herbert MR, Ziegler DA, Makris N, Bakardjiev A, Hodgson J, Adrien KT, et al. Larger brain and white matter volumes in children with developmental language disorder. Dev Sci 2003; 6: F11–22.

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, et al. Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol 2004; 55: 530–40.

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Kennedy DN, Filipek PA, et al. Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. Brain 2005; 128: 213–26.

Hiemenz JR, Hynd GW. Sulcal/gyral pattern morphology of the perisylvian language region in developmental dyslexia. Brain Lang 2000; 74: 113–33.

Hugdahl K, Heiervang E, Ersland L, Lundervold A, Steinmetz H, Smievoll AI. Significant relation between MR measures of planum temporale area and dichotic processing of syllables in dyslexic children. Neuropsychologia 2003; 41: 666–75.

Jackson T, Plante E. Gyral morphology in the posterior sylvian region in families affected by developmental language disorder. Neuropsychol Rev 1996; 6: 81–94.

Jernigan TL, Hesselink JR, Sowell E, Tallal PA. Cerebral morphology on MRI in language and learning-impaired children. Arch Neurol 1990; 48: 539–45.

Klingberg T, Hedehus M, Temple E, Salz T, Gabrieli JD, Moseley ME, et al. Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging [see comments]. Neuron 2000; 25: 493–500.

Larsell O, Jansen J. The comparative anatomy and histology of the cerebellum. III. The human cerebellum, cerebellar connections, and cerebellar cortex. Minneapolis: University of Minnesota Press; 1972.

Leach JM, Scarborough HS, Rescorla L. Late-emerging reading disabilities. J Educ Psychol 2003; 95: 211–24.

Leonard CM, Voeller KS, Lombardino LJ, Morris MK, Alexander AW, Andersen HG, et al. Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. Arch Neurol 1993; 50: 461–9.

Leonard CM, Lombardino LJ, Mercado LR, Browd SR, Breier JI, Agee OF. Cerebral asymmetry and cognitive development in children: a magnetic resonance imaging study. Psychol Sci 1996; 7: 79–85.

Leonard CM, Puranik C, Kuldau JM, Lombardino LJ. Normal variation in the frequency and location of human auditory cortex landmarks: Heschl's gyrus: where is it? Cereb Cortex 1998; 8: 397–406.

Leonard CM, Eckert MA, Lombardino LJ, Oakland T, Kranzler J, Mohr CM, et al. Anatomical risk factors for phonological dyslexia. Cereb Cortex 2001; 11: 148–57.

Leonard CM, Lombardino LJ, Walsh K, Eckert MA, Mockler JL, Rowe LA, et al. Anatomical risk factors that distinguish dyslexia from SLI predict reading skill in normal children. J Commun Disord 2002; 35: 501–31.

Lyon R, Shaywitz S, Shaywitz B. A definition of dyslexia. Ann Dyslexia 2003; 53: 1–14.

Manis F, Seidenberg M, Doi L, McBride-Chang C, Petersen A. On the bases of two subtypes of developmental dyslexia. Cognition 1996; 58: 157–95.

McArthur GM, Hogben JH, Edwards VT, Heath SM, Mengler ED. On the ''specifics'' of specific reading disability and specific language impairment. J Child Psychol Psychiatry 2000; 41: 869–74.

Misra M, Katzir T, Wolf M, Poldrack RA. Neural systems for rapid automatized naming in skilled readers: unraveling the RAN-reading relationship. Sci Stud Read 2004; 8: 241–56.

Otis AS, Lennon RT. Otis-Lennon School Ability Test (OLSAT 7), seventh edition. Orlando FL: Harcourt; 1995.

Pennington BF. Toward an integrated understanding of dyslexia: genetic, neurological and cognitive mechanisms. Dev Psychopathol 1999; 11: 629–54.

Pennington BF, Filipek PA, Lefly D, Churchwell J, Kennedy DN, Simon JH, et al. Brain morphometry in reading-disabled twins. Neurology 1999; 53: 723–9.

Plante E, Swisher L, Vance R, Rapcsak S. MRI findings in boys with specific language impairment. Brain Lang 1991; 41: 52–66.

Preis S, Jancke L, Schitter P, Huang Y, Steinmetz H. Normal intrasylvian anatomical asymmetry in children with developmental language disorder. Neuropsychologia 1998; 9: 849–55.

Ramus F, Rosen S, Dakin SC, Day BL, Castellote JM, White S, et al. Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults. Brain 2003; 126: 841–65.

Robichon F, Habib M. Abnormal callosal morphology in male adult dyslexics: relationships to handedness and phonological abilities. Brain Lang 1998; 62: 127–46.

Rumsey JM, Donahue BC, Brady DR, Nace K, Giedd JN, Andreason P. A magnetic resonance imaging study of planum temporale asymmetry in men with developmental dyslexia. Arch Neurol 1997; 54: 1481–9.

SAS. SAS/STAT guide for personal computers, Version 8. Cary NC: SAS Institute; 2002.

Semel E, Wiig E, Secord W. Clinical evaluation of language fundamentals. Third edition. New York: The Psychological Corporation/Harcourt Brace Jovanovich Inc.; 1995.

Shapiro BK. Specific reading disability: a multiplanar view. Ment Retard Dev Disabil Res Rev 2001; 7: 13–20.

Shapleske J, Rossell SL, Woodruff PW, David AS. The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. Brain Res Brain Res Rev 1999; 29: 26–49.

Snowling MJ, Adams JW, Bishop DV, Stothard SE. Educational attainments of school leavers with a preschool history of speech-language impairments. Int J Lang Commun Disord 2001; 36: 173–83.

Steinmetz H, Ebeling U, Huang Y, Kahn T. Sulcus topography of the parietal opercular region: an anatomic and MR study. Brain Lang 1990; 38: 515–33.

Stothard SE, Snowling MJ, Bishop DV, Chipchase BB, Kaplan CA. Language-impaired preschoolers: a follow-up into adolescence. J Speech Lang Hear Res 1998; 41: 407–18.

Tallal P, Miller S, Fitch RH. Temporal processing in the nervous system; implications for the development of phonological systems. Ann N Y Acad Sci 1993; 682: 27–47.

Thompson-Schill SL, Jonides J, Marshuetz C, Smith EE, D'Esposito M, Kan IP, et al. Effects of frontal lobe damage on interference effects in working memory. Cogn Affect Behav Neurosci 2002; 2: 109–20.

Thorndike RL, Hagen EP. Cognitive abilities test. Itasca, IL: Riverside Publishing; 1993.

Tisserand DJ, Pruessner JC, Sanz Arigita EJ, van Boxtel MP, Evans AC, Jolles J, et al. Regional frontal cortical volumes decrease differentially in aging: an MRI study to compare volumetric approaches and voxel-based morphometry. Neuroimage 2002; 17: 657–69.

Toga AW, Thompson PM. Mapping brain asymmetry. Nat Rev Neurosci 2003; 4: 37–48.

Turkeltaub PE, Gareau L, Flowers DL, Zeffiro TA, Eden GF. Development of neural mechanisms for reading. Nat Neurosci 2003; 7: 767–73.

von Plessen K, Lundervold A, Duta N, Heiervang E, Klauschen F, Smievoll AI, et al. Less developed corpus callosum in dyslexic subjects—a structural MRI study. Neuropsychologia 2002; 40: 1035–44.

Wechsler D. Wechsler intelligence scales for children. Third edition. New York: Psychological Corporation; 1991.

Wiederholt JL, Bryant BR. Gray oral reading tests. 3rd ed. Odessa, FL: Psychological Assessment Resources; 1992.

Wilkinson G. Wide range achievement test. Third edition. Wilmington, DE: Jastak Associates; 1993.

Wolf M, Bowers PG. The double-deficit hypothesis for the developmental dyslexias. J Educ Psychol 1999; 91: 415–38.

Woodcock RW, Johnson MB. Woodcock-Johnson psycho-education battery—revised. Chicago, IL: Riverside Publishing Co.; 1989.