Is There a Common Neuroanatomical Substrate of Language Deficit between Autism Spectrum Disorder and Specific Language Impairment?

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Discussion of an overlap between specific language impairment (SLI) and autism spectrum disorder (ASD) is on going. The most intriguing overlap between both phenotypes is the similarity in the observed language deficits described in SLI and a subgroup of ASD with co-occurring linguistic impairment, ASD-LI. Examining whether a similar neuroanatomical substrate underlies this phenotypical linguistic overlap, we studied the white matter microstructural properties of the superior longitudinal fascicle (SLF) of 19 ASD-LI adolescents (mean age 13.8 ± 1.6 years) and 21 age-matched controls and compared them with 13 SLI children (mean age 10.1 ± 0.4 years) and 12 age-matched controls. A linguistic profile assessment and a diffusion tensor imaging analysis of the SLF were performed. Linguistic testing revealed a mixed receptive–expressive disorder profile in both groups, confirming their overlap at phenotypical level. At neuroanatomical level, no significant differences in mean SLF fractional anisotropy (FA) and mean SLF apparent diffusion coefficient values between ASD-LI participants and controls were seen. By contrast, the mean SLF FA was significantly reduced in the SLI children as compared with their controls. The observation of structural SLF disturbances in SLI but not in ASD-LI suggests the existence of a different neuroanatomical substrate for the language deficits in both disorders.

Keywords: autism spectrum disorder, diffusion tensor imaging, specific language impairment, superior longitudinal fascicle

Introduction

A possible overlap between autism spectrum disorder (ASD) and specific language impairment (SLI) has been the subject of debate for more than 3 decades (Bartak et al. 1975; Williams et al. 2008). In theory, a clear distinction can be made between both disorders. SLI is defined as a failure in spoken language development, despite average nonverbal intelligence, adequate hearing and vision, absence of neurological, physical, emotional, or social problems, and adequate opportunity to acquire spoken language skills (Goorhuis and Schaarlaakens 2000; Verhoeven and van Balkom 2004). Although SLI includes children with varying profiles, arising from combinations of deficits in particular areas of communication (phonology, morphology, syntax, semantics, and pragmatics), the conventional view of SLI maintains that pragmatic skills are often intact and that the child may communicate reasonably despite having limited structural language skills. Deficits in each area can include receptive and/or expressive aspects (Conti-Ramsden and Botting 2004). In children with ASD, failure in spoken language development represents only one possible aspect of a more general problem of restricted verbal and nonverbal communication. In contrast to SLI, failure in spoken language is by convention situated in the pragmatic domain while structural language skills can be intact. In addition, children with ASD have deficits in social behavior and also present with restricted/repetitive and stereotyped patterns of behavior, interests, and activities (APA 2000).

Despite this clear theoretical distinction, in everyday practice, the diagnostic boundaries are not always that evident (Bartak et al. 1975; Conti-Ramsden et al. 2006; Leyfer et al. 2008; Bishop 2010). At the language level, accumulating evidence shows that the failure in spoken language in ASD can be a much more extensive than the apparent pragmatic deficits. Detailed linguistic studies show that the language deficits in ASD are not only restricted to the domain of language usage, prosody, understanding, and production of gestures but also encompass semantic and syntactic domains and sometimes even the phonological domain (Rapin and Dunn 2003; Groen et al. 2008). To overcome this problem, Kjelgaard and Tager-Flusberg (2001) and Bishop (2010) drew a distinction between pure ASD, SLI, and the apparent ‘comorbid cases’ who have classic autism with language impairment and are referred to as ASD-LI.

The fact that children without ASD but with a primary language disorder can present with nonstructural language impairments that are very similar to those found in ASD (Bishop 2010; Bishop and Norbury 2002) further complicates the picture. This subgroup is defined as children with pragmatic language impairment or with semantic–pragmatic disorder.
Unlike children with typical SLI, these children have adequate syntax and phonology and are often very fluent. However, they exhibit a range of linguistic and communicative (=pragmatic) deficits such as conversational inadequacies, poor turn taking, and literal interpretation of figurative language (Bishop 2000; Bishop and Norbury 2002; Conti-Ramsden and Botting 2004). It should be noted that in this subgroup, pragmatic language deficits do not occur with symptoms of impaired social reciprocity or restricted behaviors or interests.

Finally, the boundaries between the disorders are weakened by a gradual fading of the characteristic distinction between SLI and ASD over time, as was observed in a longitudinal study, performed by Bartak and colleagues (Bartak et al. 1975; Cantwell et al. 1989; Mawhood and Howlin 2000).

As a result of these findings, that is, the potential presence of structural (Kjelgaard and Tager-Flusberg 2001; Rapin and Dunn 2003; Groen et al. 2008) as well as pragmatic (Bishop 2000; Bishop and Norbury 2002) deficits in both clinical groups and the congruence of phenotypes throughout development (Bartak et al. 1975; Cantwell et al. 1989; Mawhood and Howlin 2000), several researchers have proposed that SLI and ASD-LI represent 2 expressions of the same pathology along a continuum encompassing varying degrees of language impairment. A number of studies indeed confirmed this overlap at a phenotypical level (Bartak et al. 1975; Bishop and Norbury 2002; Bishop 2003; Loucas et al. 2008; Bishop 2010).

However, it becomes quite difficult to draw any firm conclusions when looking beyond this phenotypical presentation. Family studies exploring patterns of familial transmission of language impairments show a strong heritability of structural language impairment in SLI (Bishop et al. 1996, 1999; Barry et al. 2007), whereas aggregation in the families of ASD probands is more prominent for communication difficulties than for structural language impairments (Whitehouse et al. 2007). Genetic linkage studies show different linkage signals in SLI and ASD (IMGSAC 1998, 2001; Ashley-Koch et al. 1999; APA 2000; Bradford et al. 2001; Buxbaum et al. 2001; SLIC 2002, 2004). Although these findings do not exclude a relation between both disorders, it does prevent us from drawing firm conclusions.

The present study aims at exploring the boundaries and overlaps between SLI and ASD-LI at a phenotypical and a neurobiological level. At a phenotypical level, the language profile of the participants was determined by standardized linguistic testing. For the neurobiological characterization, diffusion tensor imaging (DTI) was used. DTI, a radiological technique sensitive to the Brownian motion of water, enables the measurement of restricted and/or hindered movement of water molecules as they diffuse in the brain (Basser et al. 1994)—for a detailed review article, see Tournier et al. (2011). Based on DTI, fiber tracts can be virtually reconstructed and compared. More than 26 important WM tracts have already been described (Wakana et al. 2007; Mori et al. 2008; Verhoeven et al. 2010). Delineation protocols to reconstruct these tracts have been published and tested on their reproducibility (Catani et al. 2005; Wakana et al. 2007; Hua et al. 2008; Makris and Pandya 2008). One of these major WM tracts is the superior longitudinal fascicle (SLF) that can be considered as one of the key language tracts connecting Broca’s area and Wernicke’s area, the 2 most critical language-relevant cortical regions in the human brain (Bornkessel et al. 2005; Friederici et al. 2006; Makris and Pandya 2008; Snijders et al. 2009).

In this study, we examined the expressive-receptive language profile of participants and correlated it with the WM microstructural properties of the SLF. We hypothesized that if ASD-LI and SLI share a common etiology, a similar linguistic profile and similar underlying structural connectivity deficits in the language-processing areas of the SLF would be found.

**Materials and Methods**

**Subjects**

Nineteen participants with ASD-LI (mean age 13.8 ± 1.6 years; 16 males and 3 females) and 21 age-matched controls (mean age 14.4 ± 1.5 years; 16 males and 5 females) were included. We also included 13 children with SLI (mean age 10.1 ± 0.4 years; 10 males and 3 females) and 12 age-matched controls (mean age 10.2 ± 0.3 years; 8 males and 4 females). All participants were right-handed, native Dutch speakers with normal hearing. All the included subjects had a normal intelligence with a performance or full scale IQ above 80.

Inclusion criteria for the ASD-LI group were 1) a diagnosis of autistic disorder or pervasive developmental disorder—not otherwise specified according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR) criteria (APA 2000), 2) scores equal to or greater than 15 on the Social Communication Questionnaire (SCQ) (Rutter et al. 2003) and 3) scores above 60 on the Social Responsiveness Scale (SRS) (Constantino et al. 2003). ASD participants with a significant history of language delay/impairment, defined by the absence of 2-word combinations at the age of 3, need for intensive speech therapy during preschool years, and the presence of language problems at the time of diagnostic assessment, were specifically selected, aiming for a subgroup ASD-LI. Participants were selected from a clinical sample of children with previous diagnosis made by a multidisciplinary team including a pediatric neurologist/psychiatrist and based on the DSM-IV-TR criteria. SCQ and SRS were used to ensure the current presence of substantial ASD symptoms. Two individuals were on methylphenidate and one was on risperidone at the time of DTI acquisition. Participants were excluded if there was an important medical history or an abnormal neurological examination, if ASD-LI was associated with a genetic syndrome or if conventional MRI was found to be abnormal.

For the SLI group, participants were drawn from a longitudinal study on SLI performed at our University (Vandewalle et al. 2010). All these children were born in the year 2000 and had a history of significant language delay with otherwise normal development, for which language therapy was started in kindergarten. At the start of therapy, children scored below percentile 3 on at least one of the subtests of 3 standardized and validated Dutch language tests: “Beynll Taalontwikkelingschalen” (Schaeflaeken et al. 2005), “Taaltests voor Kinderen” (van Bon and Hoekstra 1982), or “Schlichting Test voor Taalproductie” (Schlichting et al. 2003). To ensure the persistent character of the language problem, children had to score below percentile 10 on at least one of the subtests of these language tests at a clinical evaluation after the age of 4.4 years.

Due to age incongruence between both study groups, a separate age-matched control group was composed for each study group. These healthy volunteers were actively recruited. None of them had a history of neurological or psychiatric conditions nor a current medical, developmental, or psychiatric diagnosis. They did not report any language problems. The parents of both the SLI participants and the children of the 2 control groups completed the SCQ and SRS questionnaires to exclude the presence of substantial ASD symptoms in both groups.

The study was approved by the local Ethical Board, and informed consent was obtained from all parents/guardians according to the Declaration of Helsinki, with additional assent from all participating children.

**Neurobehavioral Evaluation**

Participants were assessed with an abbreviated version of the Dutch Wechsler Intelligence Scale for Children, Third Edition (Kort et al. 2005) to estimate IQ. The abbreviated intelligence test involved the
subtests Block Design and Picture Completion to estimate a performance IQ (PIQ) and the subtests Vocabulary and Similarities to estimate verbal IQ (VIQ; Sattler 2001). The abbreviated version has been found to correlate well with a full IQ battery and has been used in other studies of cognitive ability and language (Hohnen and Stevenson 1999). The IQ scores were used to confirm normal intelligence in all participants.

The Dutch version of the Clinical Evaluation of Language Fundamentals (CELF-4-NL) (Kort et al. 2008) was used to assess the language skills of our study population. The following subtests of the CELF-4-NL were used: Sentence Formulation (SF), Sentence Assembly (SA), Word Definitions (WD), Word Classes Expressive (WCE) (expressive language subtests), Word Classes Receptive (WCR), Text Comprehension (TC), and Semantic Relations (SR) (receptive language subtests). Statistical comparison between participants and their respective age-matched controls was done using an unpaired t-test of the raw test scores. The significance threshold was set at \( P < 0.05 \) after Bonferroni correction for multiple pairwise comparisons. Due to a significant age difference between both clinical groups, a direct comparison between both groups was not possible. Therefore, \( Z \) scores standardized relative to the age-matched control group were calculated and used for between-patient group comparisons. A composite score for expressive language ability and a composite score for receptive language ability was calculated by averaging the \( Z \) scores of the constituent subtests.

**Neuroanatomical Evaluation**

**Data Acquisition**

All participants underwent MRI examination on a 3T system (Philips, Best, The Netherlands). The DTI data were acquired using an optimized single-shot spin-echo, echo planar imaging sequence with the following parameters (Jones and Leemans 2011): 68 contiguous sagittal slices, slice thickness = 2.2 mm, repetition time (TR) = 11.045 s, echo time (TE) = 55 ms, field-of-view (FOV) = 220 × 220 mm\(^2\), matrix size = 112 × 109, in-plane pixel size = 1.96 × 2.00 mm\(^2\), acquisition time = 10 min 34 s. Diffusion gradients were applied in 45 noncollinear directions (\( b = 800 \) s/mm\(^2\)) and one nondiffusion-weighted image was acquired. Two identical DTI data sets were consecutively acquired per subject to improve the reliability of the estimated diffusion measures, bringing the total acquisition time to 21 min 8 s.

Additionally, coronal 3D turbo field echo \( T_1 \)-weighted images were obtained as a series of 182 contiguous coronal slices covering the whole brain and brainstem: slice thickness = 1.2 mm, TR = 9.7 ms, TE = 4.6 ms, FOV = 250 × 250 mm\(^2\), matrix size = 256 × 256, in-plane pixel size = 0.98 × 1.20 mm\(^2\), and acquisition time = 6 min 38 s.

**Data Processing**

Raw diffusion MR data were transferred to an offline workstation. All the images were first visually inspected for the presence of apparent artefacts. Further pre- and postprocessing was done using ExploreDTI (Leemans et al. 2009). Motion and eddy current correction of the data was done according to the ROI definition protocols of Wakana (Wakana et al. 2007), which brings the number of SLI participants down to 10.

Subsequently, the diffusion tensors (DT) were estimated using nonlinear least squares fitting (note that this was performed on the concatenation—not the average—of both DTI data sets to improve the reliability of the estimated diffusion measures). Whole-brain fiber tractography was calculated for each DTI data set using a uniform 2-mm grid, point resolution, fractional anisotropy (FA) termination threshold of 0.2, angle threshold of 30\(^\circ\), and a minimal fiber length threshold of 50 mm. Region of interest (ROI) delineation for the SLF was done according to the ROI definition protocols of Wakana (Wakana et al. 2007), which showed a high reproducibility and reliability of their tract reconstruction protocols (Fig. 1). A good intrarater and interrater reliability for this tract reconstruction was confirmed in a previous study (Verhoeven et al. 2010). Scalar invariants, FA, and apparent diffusion coefficient [ADC] were determined for left and right SLF for all subjects. To detect diagnosis-related differences in FA and ADC, a general linear model analysis was performed with FA and ADC as dependent variables, respectively. Control groups (controls for ASD-LI group and controls for SLI group) and clinical groups (ASD-LI and SLI) were labeled as CO-ASD, CO-SLI, ASD-LI, and SLI, respectively. When both control groups were combined, they were referred to as CO-all. Left- and right-sided SLF, as well as subjects groups were defined as fixed factors. The significance threshold was set at \( P < 0.05 \) after Bonferroni correction for multiple testing.

**Correlation of Neuroanatomical and Neurobehavioral Data**

For the correlation of FA with behavioral measures, Pearson correlations between FA values for left and right SLF and language measures were calculated. To limit the number of comparisons, analyses were limited to the hypothesized "language-to-structure" correlation. No comparisons were performed with other behavioral measures such as SRS and SCQ scores.

**Results**

**Demographics**

An overview of the group characteristics is presented in Table 1. As previously mentioned, the ASD-LI participants (ASD-LI, \( n = 19 \)) and their controls (CO-ASD, \( n = 21 \)) were significantly older than the SLI participants (SLI, \( n = 13 \)) and their controls (CO-SLI, \( n = 12 \)). Since this age difference may cause different performance on the language tests, and since a small effect of age on WM characteristics could not be excluded as well (Hermoye et al. 2006; Lebel et al. 2008; Verhoeven et al. 2010), the SLI study group and the ASD-LI study group were treated separately. Within study groups, participants and controls were well matched for age. The VIQ of each clinical group was significantly lower than in the respective control group, reflecting the inherent language problems. In the SLI study group, participants and controls were not significantly different for PIQ. In the ASD-LI study group, the ASD-LI participants showed a slightly lower PIQ compared to the age-matched controls (\( P = 0.041 \)). All controls scored below the risk value for ASD on the SRS and SCQ questionnaires, whereas all ASD-LI children presented with SRS and SCQ values above the set risk value. In the SLI group, 2 children scored above the risk value for SRS only, and one scored above the cutoff values for both the SRS and SCQ. The latter 3 participants were excluded from further analysis to avoid inappropriate inclusion of ASD-LI participants in the SLI group, which brings the number of SLI participants down to 10.

**Language Testing**

Language skills were evaluated by an experienced speech-language pathologist on the day of scanning or in a time interval of less than 1 month prior to scanning. The duration of testing was 1.5 h. Standardized language test results could not be obtained for 3 ASD-LI participants. The results of one participant were excluded from the linguistic data set of this study because of the extensive lack of expressive language skills. The 2 others dropped out of follow-up. All other controls and SLI participants completed the selected language tests. Due to a significant age difference between both clinical groups, both groups were assessed separately. Raw test scores of the CELF-4-NL were standardized into age-independent \( Z \) scores, for statistical-between-study group comparisons. All language results are summarized in Table 2.

In the SLI study group, all SLI participants except one, scored on at least one of the language subtests below percentile 10,
confirming the persistent character of the language problems. They scored significantly poorer than their age-matched controls on every language subtest. Therefore, we could identify our ASD participants as ASD-LI participants (Bishop 2010). Across all language tests, they scored on average –1.21 standard deviation (SD, range from –2.15 to –0.26) below the level of their controls.

In the ASD-LI study group, ASD participants scored significantly poorer than their age-matched controls on every language subtest. Therefore, we could identify our ASD participants as ASD-LI participants (Bishop 2010). Across all language tests, they scored on average –2.82 SD (range from –5.04 to –2.18) below the mean of their controls. A comparison of the age-independent Z scores of the ASD-LI and SLI participants reveals significantly poorer performance of the ASD-LI participants on WD and SR.

The composite expressive language Z score and the composite receptive language Z score indicate that both the ASD-LI participants and the SLI participants show a significant failure in both expressive and receptive language. The receptive language deficit is significantly more severe in the ASD-LI group than in the SLI group.

**Imaging Results**

To exclude a possible difference in WM characteristics due to group differences in age, a Multivariate analysis of variance (MANOVA) analysis comparing both control groups was performed first. FA and ADC SLF values were entered as dependent variables and participant groups (CO-SLI vs. CO-ASD) and hemisphere (left vs. right) as fixed factors. The controls of both study groups showed no significant difference in mean SLF FA (P = 0.369) and mean SLF ADC (P = 0.553).

For further analysis, data of both control groups were collapsed and treated as one, referred to as CO-all.

Second, a MANOVA analysis was done to compare the control subjects (CO-all) with the SLI participants and the ASD-LI participants. Again, FA and ADC values were used as dependent variables, and participant groups (CO-all, SLI and ASD-LI) and hemisphere were entered as fixed factors. For FA, a significant main effect was seen for group (P = 0.002; mean FA CO-all = 0.460, mean FA SLI = 0.438, mean FA SLI = 0.459) and hemisphere (P < 0.001; mean FA right = 0.436, mean FA left = 0.469). There was no interaction effect (group × hemisphere, P = 0.948). For ADC, only a significant main effect of hemisphere was present (P < 0.001).

No significant difference was found in mean SLF FA when comparing the control subjects and the ASD-LI participants (P = 1.000). In contrast, mean SLF FA was significantly reduced (P = 0.001) in the SLI participants compared with all control subjects (Fig. 2). This difference persisted when the SLI participants were compared only with their age-matched controls (P = 0.007). A significant difference in mean SLF FA was also shown between ASD-LI participants and SLI participants (P = 0.006). No significant group differences were found for mean SLF ADC when comparing the CO-all with the ASD-LI participants nor when comparing them with the SLI participants.

Results of the multivariate linear model analysis are presented in Table 3. The mean SLF FA and mean SLF ADC values are given for each participant group (SLI, ASD-LI, and CO-all) and mean differences as well as 95% confidence intervals of the differences are shown. Figure 2 shows a box plot representation of the results.

**Correlation of FA with Behavioral Measures**

Finally, we studied the correlation between the diffusion scalar measures and the language results. Since significant diffusion differences were only found for the FA measure, the correlation

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**Table 1**

<table>
<thead>
<tr>
<th>Subject characteristics per group</th>
<th>P value between study groups</th>
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<tr>
<td></td>
<td>ASD-LI study group</td>
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<tr>
<td>AGE</td>
<td>CD-ASD</td>
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<tr>
<td>P value</td>
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<tr>
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<td>CD-ASD</td>
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<tr>
<td>P value</td>
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<tr>
<td>PIQ</td>
<td>CD-ASD</td>
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<tr>
<td>P value</td>
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<td>CD-ASD</td>
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<td>ASD-LI</td>
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<tr>
<td>P value</td>
<td>≤0.001*</td>
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<tr>
<td>SCQ</td>
<td>CD-ASD</td>
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<td></td>
<td>ASD-LI</td>
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<tr>
<td>P value</td>
<td>≤0.001*</td>
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Note: This table shows an overview of the participant characteristics age, VIQ, PIQ, and SCQ for each participant group (ASD-LI, n = 19; SLI, n = 10) and their respective age-matched controls (CO-ASD, n = 21; CO-SLI, n = 12). Mean and SD is given for each parameter. P values are given for within-study group (underneath) and between-study group (right column) comparisons. Significant differences (P < 0.05) are indicated by an asterisk.
study was restricted to this scalar value. Scatter plots were generated and Pearson correlation coefficients were calculated between each language subtest and the mean SLF FA value. No significant correlation between the language subtest results and the mean SLF FA values were found in the control group and the ASD-LI group, either for the individual language subtests or for the composite scores. In the SLI group, however, a good model fit was found for the WCR language subtest result that correlates positively with the mean SLF FA of the SLI participants on the left side (Pearson correlation = 0.638, $R^2 = 0.407$, $P = 0.047$) as well as on the right side (Pearson correlation = 0.672, $R^2 = 0.452$, $P = 0.033$) (Fig. 3a, b). A marginally significant model fit was found for the WCE language subtest result that correlates positively with the mean SLF FA of the SLI participants on the left side (Pearson correlation = 0.638, $R^2 = 0.407$, $P = 0.047$) (Fig. 3c). The right-sided SLF FA was not significantly correlated to the WCE language subtest results (Pearson correlation = 0.535, $R^2 = 0.287$, $P = 0.111$) (Fig. 3d). The correlation of the mean SLF FA of the ASD-LI participants with the WCR language subtest and the WCE language subtest results, respectively, was not significant.

**Discussion**

For several decades, an overlap between ASD-LI and SLI has been debated because of the similarities in the language profile, clinically observed in children with typical and atypical development (Bartak et al. 1975; Bishop and Norbury 2002; Bishop 2003; Loucas et al. 2008; Bishop 2010).

In this study, we explored the neurobiology of ASD-LI and SLI at the level of language impairment. Because the SLF can be considered to be a major tract for language processing connecting the receptive and expressive language areas (Bornkessel et al. 2005; Makris and Pandya 2008), the target of this study was to examine the link between the linguistic profile in ASD-LI and SLI and microstructural deficits in language-processing areas of the SLF.

ASD participants with a clear history of language impairment were included in this study. Since no recent linguistic assessment was available at the time of intake, and inclusion criteria were based on anamnestic measures, we first assessed the type and severity of the language disorder through extensive language testing of all participants. These tests confirmed the presence of a structural language deficit in the ASD participants with a significant lower performance compared with their age-matched controls. All assessed language skills were affected. This resulted in a mixed receptive-expressive language disorder profile, and we therefore could identify our ASD participants as ASD-LI participants (Bishop 2010).
In a next step, SLI participants were assessed with a similar methodology. Taking into account that the age difference between ASD-LI and SLI participants could bias our results, we selected a second control group, matched in age with the SLI group, and assessed their language skills. As with the ASD-LI participants, we observed a mixed receptive-expressive disorder profile in the SLI participants, compared to their age-matched control group. To rule out that possible neuroanatomical differences between the ASD-LI and the SLI group may result from a different degree of language failure present in both patient groups, we compared the age-independent Z scores of each subtest between ASD-LI and SLI participants. Although the ASD-LI participants generally showed a more severe language failure, the difference was only significant for the SR subtest and the WD subtest. Therefore, at this level, we can conclude that in our study too, a substantial overlap in language phenotype was present for the SLI and the ASD-LI participants.

Looking for a similar common structural basis for the language impairment, we compared the WM characteristics of the SLF in SLI and ASD-LI participants. The mean SLF FA was significantly reduced in SLI participants, indicating an abnormal microstructural organization between Broca and Wernicke in this patient group. These changes in architectural properties were not present in the ASD-LI participants, with mean SLF FA and mean SLF ADC values comparable to the controls. Despite the marked phenotypical overlap in the language deficits of both study groups, our results indicate that, at the level of the SLF, there is a clear structural distinction between SLI and ASD-LI participants.

Current evidence on the shared neurobiology of SLI and ASD is limited and controversial. De Fosse showed a significant reversal of asymmetry in the frontal language-related cortex in both ASD and SLI (De Fosse et al. 2004) indicating a neurobiological overlap of both conditions. However, in the follow-up study done by Hodge et al. (2009), same participants were found to be significantly distinct at level of the cerebellum, in the lobule VIIa Crus I (Hodge et al. 2009). This finding is important since Crus I area is a cerebellar region consistently associated with language processing.

Herbert et al. assessed brain asymmetry at several levels of parcelisation. At the cortical parcelisation level, a right:left ratio reversal in both the SLI group as the ASD group was found. However, the decrease in left asymmetrical cortex present in the SLI could not be confirmed in the autism group (Herbert et al. 2005).

Finally, a recent study by Whitehouse and Bishop (2008) measured cerebral dominance using functional transcranial doppler ultrasonography, assessing blood flow through the middle cerebral arteries. Here, the SLI group with persistent language problems presented a greater right than left hemisphere activation during a word generation task while the reverse was true for the ASD patients and the controls (Whitehouse and Bishop 2008). Collating these findings with our DTI findings, we conclude that, in addition to imaging and language similarities in ASD-LI and SLI, some important neuroanatomical differences in language-processing areas are present as well.

Interestingly, recent studies on the phenotypical overlap in the language deficits report qualitative language differences between

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**Figure 2.** A box plot representation of the mean SLF FA values in controls (CO-all), participants with SLI and participants with autism spectrum disorder (ASD-LI). The dark line in the middle of the boxes is the median of the mean FA values for each subject group. The bottom of the box indicates the 25th percentile. The top of the box represents the 75th percentile. The T-bars that extend from the boxes extend to the minimum and maximum values. The indicated P values above the box plots reflect statistical significance between the indicated study groups using a MANOVA test.

**Table 3**

Mean FA and mean apparent ADC values extracted after deterministic fiber tractography of the SLF in CO-all, SLI, and ASD-LI.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Mean difference</th>
<th>P value</th>
<th>95% Confidence interval</th>
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<tr>
<td></td>
<td>Lower bound</td>
<td>Upper bound</td>
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<tr>
<td>FA</td>
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<tr>
<td>CO-ALL</td>
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<td>SLI</td>
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<td>ADC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO-ALL</td>
<td>7.258 × 10⁻⁴</td>
<td>1.493 × 10⁻⁵</td>
<td>0.131</td>
<td></td>
</tr>
<tr>
<td>SLI</td>
<td>7.407 × 10⁻⁴</td>
<td>1.493 × 10⁻⁵</td>
<td>0.131</td>
<td></td>
</tr>
<tr>
<td>ASD-LI</td>
<td>7.259 × 10⁻⁴</td>
<td>1.484 × 10⁻⁵</td>
<td>0.220</td>
<td></td>
</tr>
</tbody>
</table>

Note: Mean differences between subject groups are calculated. The indicated P values reflect statistical significance using a MANOVA test. Significant differences are indicated by an asterisk. The 95% confidence intervals are shown in the column on the right-hand side.
SLI and ASD-LI in addition to the well-known quantitative overlap (Whitehouse et al. 2007; Lindgren et al. 2009; Riches et al. 2010). In this respect, Whitehouse et al. (2007) proposed a different origin of the disturbed language profile in SLI and ASD-LI. The detailed language data from the current study seem to further support this hypothesis. Indeed, despite the fact that both SLI and ASD-LI participants could be classified as having a mixed receptive-expressive language disorder profile, detailed analysis of the language subtest results revealed a global pattern of failure in the ASD-LI participants (failure on all subtests), while the language failure in the SLI participants was more restricted to some specific language subtests (only 3). Finally, also some noteworthy differences were found in the correlation analysis, linking the anatomical and phenotypical data. A significant positive correlation was noted between the mean SLF FA values and 2 of the significantly impaired language subtests (WCR and WCE) only in the SLI group, linking integrity of the SLF to a better performance on these subtests in the SLI group. Despite the fact that the performance of the ASD-LI participants for the same subtest was equally weak (no significant difference in Z scores ASD-LI vs. SLI), the ASD-LI participants did not show a structural deficit at the level of the SLF and no correlations with language performance could be found. These findings again support a different origin of the WCR and WCE subtest failure in both patient groups.

The linkage of microstructural deficits in the SLF to a particular aspect of language processing is complicated because each language test necessarily embeds several aspects of language. Whitehouse suggested short-term working memory problems as a possible cause of the disturbed language profile in SLI (Whitehouse et al. 2008). Short-term working memory is also an important component in the completion of the WCR task. Failure in short-term working memory is believed to be associated with structural and functional abnormalities in frontal-parietal circuitry (Karlsgodt et al. 2008). The SLF is the main frontoparietal WM connection. At the moment, it is premature to relate our findings in the SLF to these working memory problems, but this might be an interesting topic for further research. Our findings of a more global and a more severe pattern of failure in the ASD-LI participants without any repercussion on the main language tract, the SLF, might support the hypothesis that structural language deficits might arise as a part of the broader ASD phenotype. Further research on the links between language profiles and underlying structural impairments might clarify their etiological relationship.

This study has a number of limitations of which the first one relates to the rather small sample size of the SLI group. SLI at mid-childhood, however, is quite rare. Furthermore, many children contacted did no longer present with language

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**Figure 3.** (A, B) Scatter plot of Word Classes Receptive Z scores (WCR, Zscore) (x-axis) and mean SLF FA values (y-axis) in control groups (CO-SLI and CO-ASD) and patient groups (SLI and ASD-LI) at the hemisphere left (A) versus right (B). A significant positive correlation between WCR test score and mean SLF FA value was observed for the SLI patient group ($R^2 = 0.465$ for the left SLF and $R^2 = 0.454$ for the right SLF). (C, D) Scatter plot of Word Classes Expressive Z scores (WCE, Zscore) (x-axis) and mean SLF FA values (y-axis) in control groups (CO-SLI and CO-ASD) and patient groups (SLI and ASD-LI) at the hemisphere left (C) and right (D). A significant positive correlation between WCE test score and mean SLF FA value was observed only in the left hemisphere ($R^2 = 0.407$).
problems, which made it difficult to compare them with the ASD-LI participants, in whom language problems were still clearly present. We believe it will be useful to expand our data in a larger cohort, which is the scope of our future research program.

Second, the age differences between ASD-LI and SLI participants might complicate the interpretation of this study. To control for this bias, we created 2 age-matched control groups and limited statistical comparisons within groups. We also demonstrated the absence of DTI differences between the 2 age-band control groups. Assuming that development is lagged by a few years in both SLI and ASD-LI participants, one could argue the possibility of a maturational lag explaining the results. However, this possibility seems less probable since the most "matured" group (ASD) shows the most severe language failure.

Next, we should recognize that by examining the SLF as a whole, we might have lost some specificity. Recent literature has shown that the SLF is much more complex than initially assumed and can be subdivided in 3 (Catani et al. 2005) or even 5 subdivisions (Makris and Pandya 2008), all of which represent a different underlying language functionality. The segregation of the SLF in its different subcomponents might add some valuable information about disorganization at the sublevels and augment language specificity.

Finally, it is important to acknowledge the general limitations of DTI in terms of specificity. In other words, it is well known that there are many confounds, such as the partial volume effect (Vos et al. 2011) or the "crossing fibers" issue in brain regions with complex fiber architecture (Wheeler-Kingshott and Cercignani 2009) among others, which may affect diffusivity measures in a nontrivial way (Tournier et al. 2011, in press). As a result, although regarded as highly sensitive, any observed changes in DTI-based measures may be hard to interpret in an unambiguous way.

Conclusion

For several decades, SLI and ASD research has been characterized by an ongoing debate as to whether SLI and ASD-LI constitute 2 expressions of the same spectrum of disorder. The phenotypical overlap in their language deficits appears to be the most remarkable feature linking both conditions. In this article, we showed that despite this phenotypical overlap, the neuroanatomical deficit underlying the impaired language processing is not the same.

Funding

"Fund for Scientific Research-Flanders," FWO, Belgium (G.0354.06); IUAP-KUL (FWO fellowship asp/07 to J.S.V.); the Research Council (IDO/08/013).

Notes

We thank our participants and healthy volunteers that made this research possible. The authors are grateful to S. Loomans and M. Verly for their assistance with language testing. Conflict of Interest: None declared.

References


