Age-Related Brain Structural Alterations in Children With Specific Language Impairment

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Abstract: Previous neuroimaging studies have suggested that children with specific language impairment (SLI) may show subtle anatomical alterations in specific brain regions. We aimed to characterize structural abnormalities in children with SLI using a voxel-wise analysis over the whole brain. Subjects covered a wide age range (5–17 years) in order to assess the dynamic nature of the disorder across childhood. Three-dimensional MRIs were collected from 36 children with SLI and from a comparable group of healthy controls. Global gray and white matter measurements were obtained for each subject, and voxel-based morphometry (VBM) was used to evaluate between-group differences in regional brain anatomy. Possible age-related changes were assessed in separate analyses of younger (below 11 years of age) and older children. SLI patients showed larger global gray and white matter volumes, particularly in the younger subgroup. Voxel-wise analyses of the whole sample showed two regions of increased gray matter volume in SLI: the right perisylvian region and the occipital petalia. Age-group analyses suggested a more extended pattern of volume increases in the younger subjects, which included entorhinal, temporopolar, caudate nucleus, motor-precentral and precuneus gray matter, and white matter of the frontal and temporal lobes. Our results suggest that in the SLI brain there are enduring anatomical alterations that exist across a wide age range, as well as a distributed pattern of abnormalities that appear to normalize with development. They also suggest that the neuroanatomical basis of SLI may be better characterized by considering the dynamic course of the disorder throughout childhood. *Hum Brain Mapp* 30:1626–1636, 2009. © 2008 Wiley-Liss, Inc.

Key words: child and adolescent; specific language impairment; MRI; neuroanatomy; voxel-based morphometry (VBM)

INTRODUCTION

Specific language impairment (SLI) is defined as a failure to acquire age-appropriate language skills in children with normal opportunities to learn language, no obvious sensorial or neurological alterations, and with otherwise typical development [World Health Organization, 1992]. The language phenotype of children with SLI is heterogeneous, presenting with varying combinations of deficits in the expressive and receptive domains, as well as with literacy problems [McArthur et al., 2000]. Phonological processing is typically altered in SLI [Bishop and Snowling,

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2004], with both deficits in phonological memory [Gathercole and Baddeley, 1990] and phonological awareness [Snowling et al., 2000] being reported. However, language alteration is not restricted to phonology, as impairments in morphology and syntax, and poor lexical and discourse skills, have also been described [Bishop and Snowling, 2004].

The causes and biological basis of SLI are poorly understood [Webster and Shevell, 2004]. Although there are some reports of central nervous system abnormalities [Guerreiro et al., 2002; Trauner et al., 2000], brain magnetic resonance imaging (MRI) of children with SLI usually appears normal upon visual inspection. Nevertheless, subtle structural abnormalities, such as alterations of the normal (leftward) asymmetry pattern of perisylvian language-related regions, have been consistently described in group-level morphometry studies [De Fossé et al., 2004; Gauger et al., 1997; Herbert et al., 2005; Jernigan et al., 1991; Leonard et al., 2002, 2006; Plante et al., 1991]. Reports of associated volumetric alterations, however, have been notably heterogeneous. Thus, while some authors reported left hemisphere volume reductions in the pars triangularis of the left inferior frontal gyrus [Gauger et al., 1997] and in the posterior perisylvian cortex [Jernigan et al., 1991], others have described a bilateral reduction of the planum temporale [Preis et al., 1998] or a specific volume increase of the right perisylvian region [Plante et al., 1991]. Likewise, reports of white matter alterations include decreases in motor, premotor, and temporopolar regions of the left hemisphere [Jancke et al., 2007], as well as global increases in the frontal, temporal, and occipital lobes [Herbert et al., 2004]. By comparison, medial white matter structures, such as the corpus callosum, are typically unaffected [Herbert et al., 2004; Preis et al., 2000]. There are also mixed results regarding global brain volume differences, from reductions in cerebral [Leonard et al., 2002] or forebrain volumes [Preis et al., 1998], to larger global brain volumes in SLI [Herbert et al., 2003b]. In this context, automated voxel-wise volumetric methods, such as voxel-based morphometry (VBM) [Ashburner and Friston, 2000], may be useful in characterizing morphometric alterations at a higher spatial resolution over the entire brain. Indeed, this structural analysis technique has already been applied in one study with SLI patients [Jancke et al., 2007].

Neuroanatomical anomalies in SLI might also be more apparent if the disorder were considered in a developmental context. At the behavioral level, there is some evidence indicating a dynamic nature to SLI. For example, the different phenotypes of this disorder are highly variable during children's development [Conti-Ramsden and Botting, 1999], suggesting that, at a given point in time, the precise nature of the language impairment may depend on the interaction with the normal pattern of development throughout childhood [Botting, 2005; Thomas and Karmiloff-Smith, 2002]. If this is indeed the case, coexisting anatomical alterations might also manifest developmentally, as normal brain maturation is known to occur along region-specific time courses [Lenroot and Giedd, 2006].

The purpose of this study was to investigate the existence of general as well as age-related anatomical alterations in children with SLI relative to control subjects. We used VBM to study volumetric abnormalities at a voxel-by-voxel basis over the whole brain.

MATERIALS AND METHODS

Participants

Thirty-six children with SLI participated in the study. This included 24 boys and 12 girls with an age range of 5–17 years (mean $\pm$ SD of 10.58 ± 2.80 years). Four children were left-handed, which is consistent with reports of a distribution of left-handers in SLI that is not different from the normal population [Bishop, 2005]. All children were referred to the neurodevelopmental disorders unit of Sant Joan de Déu Hospital, Barcelona, due to poor school achievement and suspected language disorder, and were consecutively included at the initial or follow-up visits. SLI was defined as a disturbance in the normal pattern of language acquisition from the early stages of development that was accompanied by a normal development in other domains, and could not be attributable to neurological conditions, sensory impairments, or environmental factors [World Health Organization, 1992].

Specific neuropsychological assessment was used to substantiate a deficit in the expressive, expressive/receptive, or high order language domains, and a normal nonverbal function. According to Rapin [1996], five children fulfilled criteria for a speech programming deficit, 18 for a phonological-syntactic deficit, and eight for a lexical deficit. The remaining five children could not be exclusively classified into one particular subgroup. Language assessment included the Spanish versions of the Peabody picture vocabulary test (PPVT) [Dunn and Dunn, 1997], the Token test for children (TTFC) [DiSimoni, 1978], and the Illinois test of psycholinguistic abilities (ITPA, four subscales administered, see Table I) [Kirk et al., 1968]. In addition, the Spanish version of the Wechsler Intelligence Scale for Children (WISC-III) [Wechsler, 1991] was administered as a general intelligence test assessing both language and non-language functions. Table I presents the scores of these assessments for the whole sample of children with SLI and split by age-group (see below). In all cases, scores more than 1 SD below the population mean were considered abnormal (indicated with an asterisk in Table I). Despite the wide age range of our sample, we chose to use the same scales in all children with SLI. In children older than 12 years, adult percentiles and normative values for 12-year-old children were used in the TTFC and the ITPA subscales, respectively. In any case, this did not affect the diagnosis of SLI, which was always established before 12 years of age.

At the initial visit a parental interview was performed to identify possible relevant conditions in the medical history of the patient and the existence of a language deficit from

TABLE I. Neuropsychological performance of children with SLI

	Mean (SD)								
	Full-scale IQ ^a	Verbal IQ ^a	Perform. IQ ^a	PPVT ^b	TTFC ^b	ITPA (AA) ^b	ITPA (AC) ^b	ITPA (AR) ^b	ITPA (GC) ^b
Whole SLI sample (n = 36)	84.58* (15.89)	74.61* (13.42)	100.48 (12.72)	39.28* (8.49)	40.43 (10.47)	36.95* (7.12)	40.74 (8.90)	43.25 (8.46)	34.92* (9.90)
Younger children with SLI (n = 19)	88.83 (18.99)	78.33* (14.81)	104.33 (14.47)	41.61 (9.62)	44.62 (10.67)	35.83* (7.18)	38.20* (6.92)	41.44 (8.31)	32.11* (7.70)
Older children with SLI (n = 17)	80.33* (12.31)	69.46* (9.49)	95.15 (7.38)	36.29* (5.82)	36.80* (9.13)	40.83 (6.16)	51.67 (9.28)	50.00 (5.61)	45.42 (11.17)

IQ, intelligence quotient; ITPA (AA), Illinois test of psycholinguistic abilities (auditory association); ITPA (AC), Illinois Test of Psycholinguistic Abilities (auditory closure), ITPA (AR) = Illinois Test of Psycholinguistic Abilities (auditory reception); ITPA (GC), Illinois test of psycholinguistic abilities (grammatical closure); PPTV, Peabody picture vocabulary test; TTFC, Token test for children.

*Score more than 1 SD below the age-adjusted population mean.

^aIQ scores have a population mean $\pm$ SD = 100 $\pm$ 15.

^bPPVT, TTFC and ITPA scores are presented as T scores of mean $\pm$ SD = 50 $\pm$ 10.

the early stages of development. Exclusion criteria included global developmental delay (specifically, no children with autism spectrum disorders were selected), the presence of other relevant medical and neurological conditions, sensorial or gross motor deficits, and abnormal MRI upon visual inspection. In all cases, the parents reported no perinatal problems and a normal acquisition of the autonomous deambulation (mean $\pm$ SD, in months = 12.8 $\pm$ 2.15). Objective neurological examination was normal in 23 cases and showed motor soft signs (e.g., poor motor coordination or difficulties in sequencing of complex motor tasks) in 13 subjects.

Thirty-six healthy control subjects (24 boys and 12 girls, two left-handed) of comparable age (mean $\pm$ SD age, 10.88 $\pm$ 2.83 years; range 5–17) were selected. These subjects were neurologically intact children with normal school performance whose parents agreed to participate in an ongoing study of brain development. A neurological examination and a parental interview were performed to exclude any sensorial, psychomotor or cognitive alterations, with particular interest in detecting current deficits in the language domain and possible delays in the acquisition of language function. All MRI scans were acquired without sedation. The study was approved by the local Investigational and Ethics Committee, and written informed consent was obtained from the parents of each participant.

MRI Acquisition and Processing

A 1.5-T scanner (Signa, GE Medical Systems, Milwaukee, WI) was used to obtain a sixty-slice 3D SPGR sequence in the sagittal plane (TR 40 ms, TE 4 ms, pulse angle 30°, field of view 26 cm, matrix size 256 $\times$ 192 pixels, and section thickness between 2.4 and 2.6 mm). Imaging data were

processed on a Microsoft Windows platform using a technical computing software program (MATLAB 7; The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM2; The Wellcome Department of Imaging Neuroscience, London, UK).

All images were first checked for artifacts. Image pre-processing was automated with a MATLAB script (cg_vbm_optimized, see <http://dbm.neuro.uni-jena.de/vbm/>), which involved several processes aimed at: (a) segmenting whole brain images in native space into gray matter, white matter, and cerebrospinal fluid (CSF); (b) optimally normalizing, with linear and nonlinear deformations, each segment to a tissue specific template (during this process, images were resliced to a voxel size of 1 mm³); (c) modulating voxel values by the Jacobian determinants derived from the spatial normalization to restore volumetric information; and (d) smoothing the images with a 12-mm full width at half-maximum isotropic Gaussian Kernel. After spatial normalization (step b above), images were checked again for potential misregistration artifacts. Given the age range of our subjects, we used a pediatric template and pediatric image priors derived from a sample of 148 healthy subjects from 5 to 18 years of age [Wilke et al., 2003].

Statistical Analyses

Global volume measurements

Global gray matter, white matter and CSF volumes, obtained from the original non-normalized images, were compared by univariate ANCOVA, with age and gender as covariates. Pearson's correlations were used to assess the

relationship between age and tissue volumes in patients and healthy controls. SPSS (v.15) was used in these analyses.

Regional volume analysis

SPM2 tools were used for voxel-wise analyses. Between groups comparisons were conducted separately for gray and white matter, with age and gender as covariates. Each comparison generated two *t* statistic maps corresponding to volume decreases and increases. Regional differences were reported as significant at $P < 0.05$ after correction for multiple comparisons throughout the brain, although, for displaying purposes, results were presented at threshold $P < 0.001$, uncorrected. Significant results were overlaid onto a representative normalized brain image to assist in the anatomical localization of findings.

Relationships with age were assessed in SPSS by performing Pearson's correlations between subject's age and the values of the peak voxels from the former analyses. ANCOVA tests, with group and age as independent variables (and also controlling for gender), were performed to assess for the potential between-group differences (i.e., group $\times$ age interactions) in the relationship between regional tissue volumes and age.

SLI subgroup analysis and correlations with neuropsychological scores

Firstly, as the phonological-syntactic subgroup was the most prevalent in our sample, we performed an SPM conjunction analysis to assess for potential differences between this subgroup and both the rest of SLI subjects and the healthy control group. Secondly, the scores of the different neuropsychological scales were entered as regressors of interest in independent SPM analyses performed with the SLI subjects. Age and gender were entered as covariates in all these analyses. After an exploratory whole-brain assessment, small volume correction (SVC) procedures were used to restrict the analyses to the regions where anatomical alterations were detected in our sample of SLI.

To further explore the influence of age, groups were split according to the mean age of the sample, below and above 11 years. This specific cut-point differentiates two groups of subjects in both educational and developmental terms: primary (children) and secondary (adolescents) school students. All the above analyses were repeated separately for these subgroups of younger and older subjects. Independent-samples T tests (within SPSS) were used to compare the neuropsychological performance between these two age groups.

RESULTS

Neuropsychological Assessment

Scores more than 1 SD below the population mean in the language and intelligence assessment are indicated in

Table I for the whole sample of children with SLI and for the two age groups. Although these abnormal scores were only present in one of the two age groups in six scales, between-group differences were not significant after applying the Bonferroni correction for multiple comparisons.

Global Volume Measurements

Children with SLI showed larger gray and white matter volumes than controls, but no differences were observed in CSF spaces (see Table I). Gender effects (boys showing larger volumes) were significant for both gray and white matter [$F_{(1,67)} = 25.01$; $P < 0.001$; and $F_{(1,67)} = 26.68$; $P < 0.001$, respectively], although no group $\times$ gender interaction was found. Significant linear correlations between age and gray matter were observed in healthy controls [$r = 0.42$; $n = 36$; $P = 0.01$], but not in children with SLI [$r = 0.09$; $n = 36$; $P > 0.05$], which resulted in a near significant group $\times$ age interaction [$F_{(1,67)} = 3.36$; $P = 0.07$]. Global white matter was significantly correlated with age in both control subjects [$r = 0.58$; $n = 36$; $P < 0.001$] and children with SLI [$r = 0.35$; $n = 36$; $P = 0.04$].

Age effects were further assessed by analyzing the younger and older children subgroups separately. Global gray matter was increased in younger children with SLI ($n = 19$) in comparison with younger control subjects ($n = 14$), but this difference was not observed in the older children subgroup (SLI, $n = 17$; Control subjects, $n = 22$). A similar scenario was observed for global white matter, with significant differences only observed between the younger children. These results are summarized in Table II.

Regional Volume Analysis

A whole-brain voxel-wise analysis including all subjects indicated that children with SLI had increased gray matter volume in two cortical regions (see Fig. 1): the right perisylvian region (Brodmann area (BA) 22) [$t = 4.89$; $df = 68$; corrected $P = 0.04$; cluster size = 45 voxels], and the occipital petalia, in the left middle occipital gyrus (BA 18) [$t = 4.83$; $df = 68$; corrected $P = 0.04$; cluster size = 30 voxels]. No significant correlation with age was observed for the volume of these regions in either the patient and control groups. Likewise, no significant voxel-wise volumetric changes were observed in white matter.

The influence of age on regional volumes was explored further with separate voxel-wise analyses for the younger and older children subgroups. In the younger children, we observed several regions of gray matter increase in SLI (see Fig. 2A and Table III), including the entorhinal area bilaterally, and the temporopolar cortex, the caudate nucleus, the motor-precentral cortex, and the precuneus of the left hemisphere. No significant changes were observed in the older subgroup. These results were confirmed by significant group $\times$ age interactions (see Tables III and IV). Interestingly, we also observed that the most medial aspect

TABLE II. Differences in global gray matter, white matter and CSF volumes between SLI and healthy children

	SLI, Mean (SD)	Healthy controls, Mean (SD)	<i>F</i>	<i>P</i>
Gray matter				
Whole sample	802.17 (63.86) ml	771.56 (80.33) ml	5.42	0.02
Younger children	809.46 (64.11) ml	734.00 (79.75) ml	10.09	0.004
Older children	794.03 (64.54) ml	795.46 (72.66) ml	0.047	ns
White matter				
Whole Sample	371.80 (40.19) ml	354.22 (49.09) ml	4.88	0.03
Younger children	363.75 (37.98) ml	318.65 (42.08) ml	12.95	0.001
Older children	380.80 (41.81) ml	376.85 (39.24) ml	0.05	ns
CSF				
Whole Sample	280.08 (41.09) ml	289.47 (34.04) ml	0.00	ns
Younger children	283.45 (47.24) ml	274.53 (30.86) ml	2.90	ns
Older children	276.30 (33.97) ml	298.98 (33.14) ml	2.05	ns

CSF, cerebrospinal fluid; ml, millilitres; ns, nonsignificant.

of the left middle occipital gyrus showed a specific volume increase in the subgroup of younger children with SLI [$t = 5.46$; $df = 66$; corrected $P = 0.01$; cluster size = 176 voxels; interaction with age: $F_{(1,67)} = 6.94$, $P = 0.01$ (see Fig. 2A)]. Figure 3 depicts the relationship between gray matter volume and age for two representative areas: the right perisylvian region, that in comparison to controls, was increased during the whole age range (i.e., no interaction between gray matter volume and age), and the left temporopolar cortex, with a specific volume increase in younger children with SLI (i.e., interaction between gray matter volume and age).

Age specific analyses were also performed for white matter. Significant volume increases were observed in younger children with SLI in the juxtacortical white matter of the right medial frontal cortex [$t = 5.05$; $df = 66$; corrected $P = 0.01$; cluster size = 37 voxels], and bilaterally in the middle temporal gyrus [right: $t = 4.79$; $df = 66$; corrected $P = 0.02$; cluster size = 40 voxels; left: $t = 4.54$; $df = 66$; corrected $P = 0.04$; cluster size = 25 voxels (see Fig. 2B)]. No significant changes were observed in the older children subgroup. Age $\times$ group interaction was significant for all the above regions [$F_{(1,67)} = 5.27$, $P = 0.02$ for the right medial frontal cortex; and $F_{(1,67)} = 10.36$, $P = 0.002$ and $F_{(1,67)} = 5.82$, $P = 0.02$ for the right and left middle temporal gyrus, respectively]. See Table IV for group specific correlations between white matter volumes and age.

SLI Subgroup Analysis and Correlations With Neuropsychological Scores

An exploratory SPM conjunction analysis did not find any volumetric changes specifically affecting the phonological-syntactic subgroup (the most prevalent in our sample) in comparison with both the rest of SLI subjects and the healthy control group. Neither were differences observed when the analysis was repeated and restricted (using SVC procedures) to the regions shown to be increased in our

sample of SLI, even when such analyses were split by age group.

The scores of the different tests administered to the SLI subjects were entered as regressors of interest in different SPM analyses. We did not find any significant relationship with brain anatomy for the whole sample of subjects and for the two age groups. When the analyses were restricted to the regions increased in our sample of SLI, significant negative correlations were observed, in the older subjects subgroup, between verbal IQ and the right perisylvian region [$t = 4.24$; $df = 30$; SVC $P = 0.01$], and between PPTV score and the occipital petalia [$t = 4.73$; $df = 30$; SVC $P = 0.001$]. The relationship between these variables is depicted in Figure 4.

All the above analyses were repeated excluding the left-handed subjects with no relevant changes in the results.

DISCUSSION

In the present study, we observed global increases in gray and white matter volumes in the brains of children with SLI. These global changes were the consequence of a specific brain parenchyma increase in the younger SLI subgroup, whereas older subjects demonstrated no significant group differences. Regional specificity to our findings was provided by a voxel-wise analysis. For the whole sample, two clusters of cortical gray matter increase were detected; in the right perisylvian region and in the occipital petalia. In addition, when we investigated for regional changes in the younger and older children subgroups, we observed an extended pattern of regions showing gray and white matter volume increases in younger children with SLI, but not in the older subjects.

Global white matter and brain parenchyma increases have been previously reported in SLI [Herbert et al., 2003b, 2004]. Nevertheless, to our knowledge, this is the first study to report a global gray matter increase in this population of children. Although this discrepancy with previous studies may be partially explained by differences

Figure 1.

Areas of gray matter volume increase in the whole sample of children with SLI superimposed on a rendered normalized brain. (a) Right perisylvian region. (b) Left middle occipital gyrus. Color bar represents the *t* value. Voxels with $P < 0.001$ (uncorrected) are displayed.

in the sample selection (e.g., we have not exclusively included patients from the phonological-syntactic subgroup), it is important to emphasize that such studies have typically assessed gray matter volume as different components (e.g., cortex, diencephalon or cerebellum), which may have resulted in less statistical power to detect overall

volumetric changes. Volume increases in gray and white matter have also been described in other neurodevelopmental disorders, such as autism [Carper et al., 2002; Courchesne et al., 2001; Herbert et al., 2003a], suggesting that enlarged brain parenchyma may be a nonspecific feature of different, though probably related [Kjelgaard and

A. Gray matter

B. White matter

Figure 2.

Areas of gray (A) and white (B) matter volume increase in the subsample of younger children with SLI superimposed on selected slices of a normalized brain. **A:** (a) Bilateral entorhinal cortex and left temporopolar cortex; (b) left caudate nucleus and the most medial aspect of the left middle occipital gyrus; (c)

left motor cortex; (d) left precuneus. **B:** (a) Right middle temporal gyrus; (b) right medial frontal cortex; (c) left middle temporal gyrus. Color bar represents the *t* value. Voxels with $P < 0.001$ (uncorrected) are displayed.

TABLE III. Areas of gray matter volume increase in younger children with SLI in comparison with younger control subjects

Location	Brodmann area	<i>t</i> value	Corrected <i>P</i> value	Cluster size (voxels)	<i>F</i> value (interaction with age)	<i>P</i> of the interaction
Right entorhinal area	28/34	5.46	0.01	819	5.38	0.02
Left entorhinal area	28/34	4.98	0.03	275	5.05	0.03
Left temporopolar cortex	38	5.07	0.02	257	8.41	0.005
Left caudate nucleus	—	4.94	0.03	40	8.01	0.01
Left motor cortex	4	4.84	0.04	19	13.58	< 0.0005
Left precuneus	7	5.10	0.02	116	6.93	0.01

Tager-Flusberg, 2001; Rapin and Dunn, 1997], neurodevelopmental disorders. Interestingly, in autism, overall volume enlargements also appear to be more prominent in younger subjects [Carper et al., 2002; Courchesne et al., 2001].

Voxel-wise analyses were used to map the regional distribution of these global volume enlargements, and to investigate whether specific changes may exist in language-related regions. Importantly, as voxel values were unadjusted for global volume, these results show the brain regions of the largest and most consistent between-group differences in the context of a global volume increase. One area identified was the perisylvian cortex, which has been consistently related to SLI in the form of an atypical asymmetry pattern [Gauger et al., 1997; Jernigan et al., 1991; Leonard et al., 2002, 2006; Plante et al., 1991]. Our finding of a volume increase in the right perisylvian region is in agreement with some of these studies [Plante et al., 1991], and suggests that unilateral volume increases, rather than decreases, may cause the abnormal asymmetries reported in SLI. Another region detected was the occipital petalia. In this case, however, the left side volume enlargement represented a larger expression of the typical leftward asymmetry of this region [Hervé et al., 2006]. Although the relationship of this last finding with language function is difficult to establish, such results suggest that in SLI normal asymmetry patterns may be reversed at the level of particular cortical regions (i.e., the perisylvian region),

rather than in gross neuroanatomical patterns (i.e., the brain torque), as previously reported [Herbert et al., 2005].

Separate voxel-wise analyses for the younger and older SLI subjects allowed us to identify brain regions specifically enlarged in the younger subgroup. We observed volume increases in the left temporopolar cortex and, bilaterally, in the white matter of the middle temporal gyrus. Left temporopolar cortex has been related to language comprehension, possibly as part of a memory network for encoding and retrieval of linguistic material [Vigneau et al., 2006]. White matter tracks of the ventral part of the temporal lobe have also been proposed as part of this system by providing input from posterior occipitotemporal regions to the temporal pole [Duffau et al., 2005]. Interestingly, this ventral processing stream, which is essential for linking phonology with semantics, appears to be bilaterally organized [Hickok and Poeppel, 2007], which is in line with our finding of white matter increases in both temporal lobes. Beyond this region, other structures with volumetric changes in our younger subgroup have also been related to language function. The left precuneus, for example, has been shown to participate in auditory comprehension tasks [Schmithorst et al., 2006], and activity in the left caudate nucleus has been related to the level of accuracy in phonological processing [Tettamanti et al., 2005]. Caudate nucleus volume has also been shown to be bilaterally altered in the members of the KE family affected by a severe developmental disorder of speech and language

TABLE IV. Pearson's correlations (and *P* values) between age and regional volumes in areas increased in younger children with SLI

	Right EA	Left EA	Left TPC	Left CN	Left MC	Left PC	Right MFC	Right MTG	Left MTG
Children with SLI (<i>n</i> = 36)									
Age	0.09 (ns)	0.03 (ns)	−0.02 (ns)	−0.24 (ns)	−0.34 (0.04)	−0.35 (0.04)	0.07 (ns)	0.10 (ns)	0.11 (ns)
Healthy controls (<i>n</i> = 36)									
Age	0.52 (0.001) ^a	0.51 (0.002) ^a	0.51 (0.001) ^a	0.39 (0.017)	0.43 (0.009)	0.24 (ns)	0.49 (0.003) ^a	0.58 (<0.001) ^a	0.55 (0.001) ^a

CN, caudate nucleus; EA, entorhinal area; MC, motor cortex; MFC, medial frontal cortex (white matter region); MTG, middle temporal gyrus (white matter regions); ns, nonsignificant; PC, Precuneus; TPC, temporopolar cortex.

^aSignificant after Bonferroni correction for multiple comparisons.

Figure 3.

Relationship between gray matter volume and age in two representative locations. (a) In the right perisylvian region, Pearson's correlation was positive, although not significant, in both groups.

(b) In the left temporopolar cortex, correlation was significant only in the healthy controls group, resulting in a significant age $\times$ condition interaction (see Tables III and IV for details).

Figure 4.

Relationship between gray matter volume and neuropsychological scores in the younger and older children with SLI. (a) In the right perisylvian region, a negative relationship with verbal IQ

was observed in the older children with SLI ($r = -0.72$). (b) In the occipital petalia, a negative relationship with the PPVT score was observed in the older children with SLI ($r = -0.81$).

[Vargha-Khadem et al., 1998], although, contrary to our results, in the sense of a volumetric reduction. The relationship of this volume decrease with language function; however, is not totally understood [Liégeois et al., 2003; Watkins et al., 2002]. Changes in other brain areas of our subjects might relate more indirectly to language abilities, perhaps as a consequence of large-scale system reorganization due to impaired language capacity. Nevertheless, they may also respond to the same underlying causes of the disorder, which is not fully specific of language function, as subtle alterations in motor ability and other cognitive domains have been described [Webster et al., 2006].

The findings of our study suggest that in SLI there are discrete and long-lasting volumetric changes (e.g., in the right perisylvian region) that may coexist with a more extended pattern of abnormalities that normalize throughout development. Although, in general terms, our data are consistent with clinical observations regarding the good outcome of a subgroup of children with SLI during adolescence, even in these cases isolated phonological and reading skill deficits typically exist [Stothard et al., 1998]. In addition, in our sample, older children with SLI showed no evidence of improvement in verbal function when compared to the younger subgroup (see Table I). This is not surprising considering that our older children with SLI still required medical and psychological assistance. Interestingly, the anatomical changes in this age-group, but not in the younger children, were correlated with language impairment (see Fig. 4), suggesting that in younger children with SLI anatomical changes, albeit more extended, do not directly express the degree of language disturbance. At the youngest ages, general educational and developmental factors may strongly influence the assessment of language function, which may even present periods of “illusory recovery,” where performance of children with SLI in particular domains is similar to that of their age-peer controls [Bishop and Snowling, 2004; Scarborough and Dobrich, 1990]. In any case, significant individual differences exist in the outcome of SLI at adolescence, and, as such, further investigation is needed to elucidate which anatomical changes are present in good outcome children with SLI and the extent to which poor outcome may be predicted by the amount of anatomical alteration existing during early childhood. All in all, our data strongly suggest that the neuroanatomical basis of language function in SLI may be better characterized by considering the dynamic course of the disorder throughout children’s development [Thomas and Karmiloff-Smith, 2002].

Brain volumetric anomalies in SLI are thought to begin postnatally during the first years of life [Herbert et al., 2004]. During these years, a number of progressive and regressive events take place, and the balance between them leads to the final volume of different brain structures. According to our data, in SLI an imbalance may occur between progressive (e. g., accelerated white-matter myelination) and regressive (e.g., delayed relative reduction of gray matter) events. Although in most brain regions these

changes normalize over time, in others they seem to be long lasting. Even though some molecular mechanisms accounting for these volumetric changes may be suggested (e.g., increased neuronal size and arborization, synaptic density, or myelination), their precise characterization will require the use of other research methods in addition to MRI. Because of its limited spatial resolution, MRI volumetric measures may reflect neuronal, glial or vascular changes [Toga et al., 2006]. In this sense, the use of high resolution images may increase the ability to precisely characterize disease associated patterns of subtle structural alterations. Therefore, the relatively high slice thickness used here, despite providing accurate tissue segmentation [Pujol et al., 2002], may be considered as a study limitation. Nevertheless, anatomical MRI has been successfully applied to the study of brain maturation, especially within longitudinal designs [Giedd et al., 1999; Toga et al., 2006]. Unlike these studies, our cross-sectional assessment did not involve scanning subjects at multiple time-points. The longitudinal assessment of both patients and controls may probably lead to a more accurate characterization of the temporal dynamics of the volumetric changes in SLI.

CONCLUSION

In summary, we have described global and regional volumetric increases in gray and white matter of children with SLI. In younger children with SLI, such changes were more prominent, although they appear to normalize with age, suggesting an early neurodevelopmental alteration. In older children with SLI there were fewer volumetric alterations, albeit more directly related to the degree of language impairment. In general terms, our findings are consistent with clinical observations regarding the dynamic nature of the disorder, and emphasize the need to consider the influence of age when assessing the neuroanatomical basis of developmental language disorders.

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