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Less developed corpus callosum in dyslexic subjects—a structural MRI study

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Abstract

Background: Based on previous studies and due to the characteristics of dyslexia as an auditory phonological decoding disorder, we predicted that the shape of the posterior corpus callosum (CC) would differ between dyslexic and control subjects. *Method*: Twenty right-handed boys with developmental dyslexia were selected from a carefully screened general population sample (mean age 11 years) and compared to a matched control group. The CC contour was manually traced on the aligned midsagittal MR slice and total callosal area and its subregions were compared between the groups. A statistical shape analysis and subsequent CC classification was performed using a recently developed shape model method. *Results*: The shape analysis revealed shorter CC shape in the dyslexic group, localised in the posterior midbody/isthmus region. This region contains interhemispheric fibers from primary and secondary auditory cortices. A shape length difference larger than a fixed threshold in the posterior midbody region could correctly discriminate between control and dyslexic subject in 78% of the cases, where a dyslexic CC was shorter in this region than a control CC. However, there were no significant group differences with respect to overall CC area or subregions. *Conclusion*: A clear shape difference in the posterior midbody of the CC was found between dyslexic and control subjects. This fits with recent other studies that have reported a strong growth factor in this CC region during the late childhood years, coinciding with literacy acquisition. Our results show that the dyslexic group has not undergone the same growth pattern as the normal reading group.

Keywords: Corpus callosum; Dyslexia; Brain development; Morphometry; Shape analysis

1. Introduction

Recent genetic, brain morphology and functional imaging studies (see [1] for review) have shed light on the neurodevelopmental origin of dyslexia. A biological basis is suggested with subsequently affected neurocognitive processes. Due to the important role of interhemispheric transmission of visual and auditory information in reading, several studies have hinted towards the role of the corpus callosum (CC) and interhemispheric transfer of information in dyslexia [2,3], see also [4] for a review. Case studies have moreover indicated that patients with callosal agenesis are more impaired in phonological reading [5]. Finally, Summerfield and Michie [6] reported that interhemispheric transfer and sequential processing of dyslexic 9-year-old children was comparable to or worse than the performance of 7-year-old control children.

The slow anterior to posterior myelination of fibres in the CC during childhood suggests an ongoing developmental process to establish efficient communication between the hemispheres [7,8]. This maturation is consistent with the increment of complex neuropsychological abilities and maturation of the corresponding cortical areas. Light-microscopic examination of the CC has revealed a consistent pattern of regional differentiation of the fibre types in the CC, with large diameter fibres showing a peak of density in the posterior midbody [9]. Fibres in this area connect the primary and secondary auditory cortical areas [10]. Thompson et al. [11] investigated growth patterns in the developing brain by warping algorithms, and followed the CC development of the same individuals from 7 to 11 years of age. They found

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a striking regional growth throughout the CC with peak values occurring in this area (isthmus).

Several studies have looked for structural CC abnormalities in dyslexic subjects, however with inconsistent results. A look at these studies indicates wide variations in the subjects' age, sex, handedness, and with respect to study setting (for review see [4,12]). Most of the studies also only investigated size differences of the CC. For example, Larsen et al. [13] failed to detect structural differences in the CC of adolescent dyslexics and controls. Similarly, Pennington et al. [14] analysed the brain morphology of 75 dyslexic adolescent twins and controls matched for gender, handedness and IQ. No abnormality, either for overall CC size or for subregions of the CC was found in the dyslexic group.

Njiokiktjien et al. [15], on the other hand, compared children with developmental dysphasia and dyslexia to a heterogeneous clinical group of children with learning disabilities. They found that dyslexic subjects with a hereditary disposition had an abnormally large CC compared to non-familial cases. Hynd et al. [16], however, found a smaller genu region in the dyslexic children compared with the control subjects. Finally, Duara et al. [17] and Rumsey et al. [18] reported enlarged posterior part of the CC in adult dyslexics.

To our knowledge, only Robichon and Habib [19] compared the size and explicitly also the shape of the CC in a group of adult dyslexics and a control group. An interesting finding was that the two groups differed with respect to the shape of the CC, with the dyslexic subjects exhibiting a more circular and rounded callosal shape than the control subjects. See also Robichon et al. [20] who reanalysed the previous data with a new angulation technique that permits the analysis of CC position in the brain, and found a lower situated CC in dyslexics.

Studies also have differed with regard to the applied MR technique as well as analysis method (e.g. slice thickness and determination of the midsagittal slice for CC measurement) [21]. No anatomical landmarks show where fibres from the corresponding cortical areas cross in the midsagittal view of the CC. Therefore, methods for subdivision of the CC have varied between studies.

Due to the inconsistent findings in previous studies, we wanted to compare both shape and size in a population-based sample of 20 right handed dyslexic boys and 20 controls from the same school classes as the dyslexic subjects, with a CC manual contour tracing technique and a new shape analysis method. Thus, the groups were comparable with respect to age, gender, handedness, factors known to influence CC development [22–24]. Since dyslexia may be considered a phonological decoding disorder [25], we hypothesised that the region of the CC containing the auditory fibres, namely the posterior midbody/isthmus region, would be of particular interest. Fibers from the language areas in the superior temporal gyrus (Wernickes' area, planum temporale) pass through the isthmus area [26].

In order to explore differences in CC fibre growth patterns we compared the representative (average) CC shapes of the dyslexic and the control group, respectively. The shape prototypes were aligned with respect to the similarity group of planar transformations (scaling, rotations and translations) in a Procrustes analysis. Such an approach has been used in other CC shape comparison studies [27,28]. Constructing of shape prototypes has attracted considerable interest [29,30], but practical methods for computing such prototypes are somewhat scarce. This is mainly due to the fact that the statistical shape theory [29,30] can only be applied to sets of points of equal cardinality between which point correspondences have been established. However, in most instances, the data consist of a set of contours with different point counts and no known point correspondences. We used a new method for automatic shape alignment and prototype computation that has been developed by Duta et al. [31,32] which overcomes the need for manual point correspondences. This allows to draw conclusions regarding latent morphological features of the CC in a sample of CC contours in shape space [33].

2. Methods

2.1. Subjects

The children were recruited from the 12 largest elementary schools in the city of Bergen [1] [34,35]. Informed consent was obtained from children and parents for each successive stage of the screening procedure according to the declaration of Helsinki and the regional ethical committee had approved this study before its start. All children were in the fourth grade at the beginning of the study. To increase the number of subjects, the screening was repeated the next year in four of the schools. Children who did not learn Norwegian as their mother tongue were excluded. A total of 950 children participated in the first stage of the screening, which consisted of a spelling test with 40 real words.

In the second stage of the screening, children with scores below the 10th percentile on the spelling test were given the KOAS reading test [36]. KOAS is a computerised test-battery tapping orthographic, as well as phonological decoding strategies in reading. It is standardised for a Norwegian sample. A mean reading score for the five tasks of at least 2 S.D. below the mean age level was required for a child to be classified as reading disabled in the present study. Thirty-five children met this criterion. In addition, the children had to have an IQ of at least 85, as assessed from four verbal (information, similarities, arithmetic and vocabulary), and four performance subscales (picture completion, picture arrangement, block design and

[1] The present study was part of a larger study on brain markers of dyslexia conducted at the University of Bergen [34], headed by Prof. Hugdahl.

Table 1
Sample characteristics, mean values (range)

	Dyslexic group, $n = 20$	Control group, $n = 20$
Age in months	142 (130–149)	141 (126–149)
Full scale IQ	104 (92–126)	114 (89–138)
Verbal IQ	103 (87–126)	114 (91–133)
Performance IQ	103 (87–120)	111 (80–136)
Number of right hand tasks	11.3 (9–12)	11.6 (9–12)
Reading score (%)	68 (46–80)	96 (93–99)

coding) from the WISC-R [37]. Handedness was determined according to Annett's 12-items inventory [38]. A child was, however, classified as right-handed when this hand was used for at least 9 of the 12 tasks. None of the children had a neurological disease or trauma, or had been diagnosed with or treated for emotional or behavioural disorders.

Two children were excluded because of a hearing loss, one because of a major visual impairment, and two because of low IQ. Three children declined to participate further at this stage of the study, and one child could not enter the MR scanner due to manifestations of claustrophobia. One child with an arachnoidal cyst was excluded after the MR images had been examined by a neuroradiologist. To avoid a possible confounding effect of gender only boys were included. The final dyslexic group consisted therefore of 20 right-handed boys. Four children in the dyslexia group had received speech therapy in the pre-school period. The control group consisted of 20 right-handed boys recruited from the same school classes as the dyslexic boys, reading at or above the mean age level, otherwise meeting the same criteria as the dyslexic group. The groups differed in full scale IQ as well as in verbal IQ, with the dyslexics scoring lower than the controls as shown in the sample characteristics in Table 1.

2.2. MRI scanning

Brain imaging data were obtained by MRI scans from a Siemens Impact 1.0 T MR scanner using whole head, ear-to-ear, multispectral 3D gradient echo acquisitions (T1W FLASH TR = 22 ms, TE = 6 ms, FA = 30°; T2W DESS TR = 26, TE = 9.45, FA = 40; PDW FISP TR = 23, TE = 10, FA = 15; FOV = 256 mm, 3D slab = 160 mm, with a voxel size of 1 mm × 1 mm × 1.25 mm). The selection of the three pulse sequences was based on a previous multispectral tissue classification study [39].

From each multispectral data set, the T1-weighted 3D FLASH channel was selected for the CC analysis because of superior signal-to-noise ratio and grey matter/white matter contrast. Total MR acquisition time did not exceed 30 min. The children had been prepared for the scanning procedure by an experienced child and adolescent psychiatrist.

2.3. Measurement of CC area

In each subject, the morphometric analysis was based on the CC outline in a midsagittal slice from the 3D FLASH image volume. Each 3D data set was subject to anterior commissure–posterior commissure (AC–PC) alignment using the AFNI software package [40]. This was applied to eliminate variability in CC shape and cross-sectional area because of individual differences in head position in the scanner and the orientation of the scan plane used to generate the midsagittal image [21].

After determining the midsagittal slice in the AC–PC aligned 3D FLASH image the outline of the CC was manually traced using the specially designed program in the XITE software package [41] for outlining regions of interest. The total area (in mm^2) of the CC region was calculated as the number of pixels inside the closed contour multiplied by the pixel size. In order to reduce bias and operator-dependent variability related to the tracing procedure, the MR images were blinded for group and two independent assessors traced each CC twice.

The total midsagittal callosal area was automatically subdivided into seven subregions after having manually chosen the inflexion point at the anterior point of the inner convexity. This subdivision was identical to that of Witelson [24]. The maximal length of the CC was measured parallel to the AC–PC line [42] to allow inter-individual comparisons. The CC was then divided into halves, thirds and the posterior fifth with the following regions: A1 (rostrum), A2 (genu), A3 (rostral body), A4 (anterior midbody), A5 (posterior midbody), A6 (isthmus), A7 (splenium), as shown in Fig. 1.

Overall brain size was controlled for by indexing the midsagittal cortical brain area, as has been done in previous studies [17,18].

The midsagittal area was delimited by tracing the superior border of the CC from the genu to the splenium and then following the cerebrum posteriorly along the inferior border of the occipital lobe and continuing anteriorly over the convexity of the brain. Finally, we traced posteriorly along the inferior border of the frontal lobe until the genu of the CC was reached again (see Fig. 2).

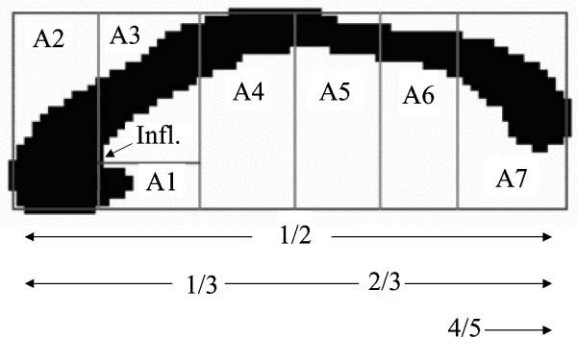


Fig. 1. Subdivision of the CC according to [24].

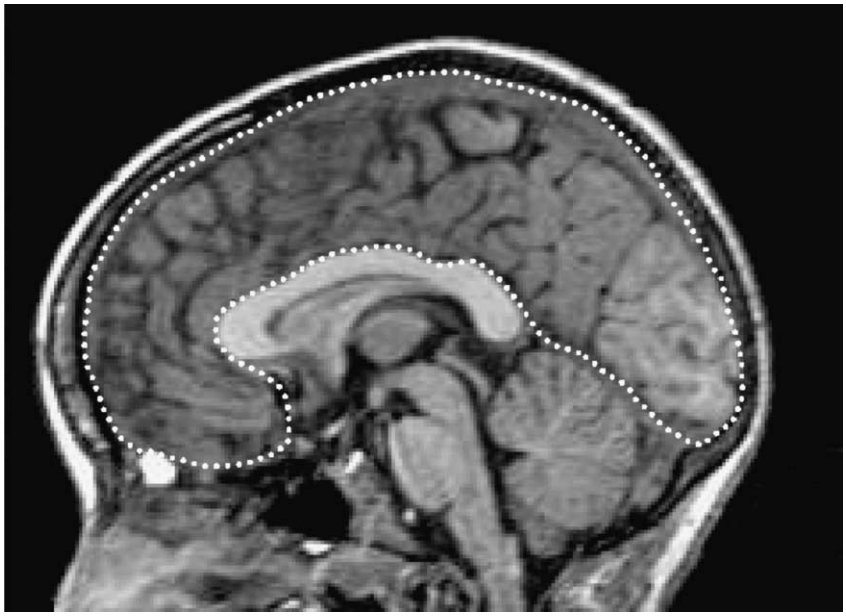


Fig. 2. The midsagittal brain area.

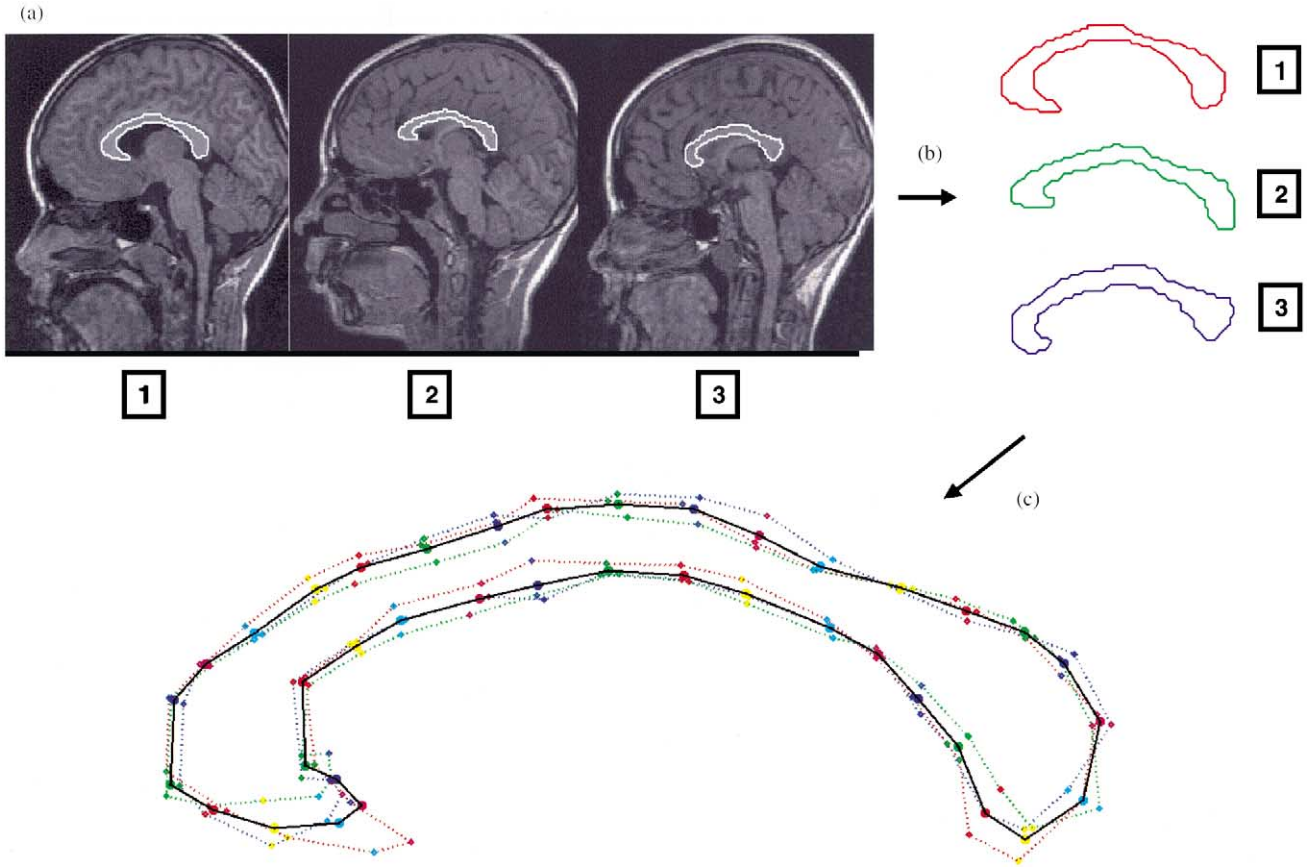


Fig. 3. Learning the shape of the CC in midsagittal (AC–PC aligned) images. (a) Manual tracings of CC performed on three subjects; (b) isolated CC contours; (c) shape prototype (black) along with statistical information about shape variation. The prototype vertices (coloured circles) have been obtained by averaging the co-ordinates of the corresponding vertices on the three examples (drawn as coloured diamonds) after they have been aligned into a common co-ordinate frame (shape space). The three aligned CC shapes are shown in dotted red, green and blue lines. This method for obtaining a prototype is called Procrustes analysis.

2.4. Statistical analyses

The groups were compared with respect to the values of the total area and of each of the seven subregions using Student's *t*-test. The level of significance was set to 0.05. The values of the total midsagittal brain area and of the ratios (midsagittal brain area/CC area) for both groups were also compared using *t*-tests. The inter- and intra-rater reliability was determined with Pearson's intraclass correlations.

To investigate if a combination of multiple CC subregion areas (A1, . . . , A7) could discriminate between dyslexic CC and control CC, we employed a simple "leaving-one-out" pattern classification design (e.g. [43]). For each subregional combination we defined, subject by subject, a feature vector consisting of the calculated areas of the corresponding CC subregions. We thus extracted 40 labelled feature vectors, 20 belonging to the control group and 20 to the dyslexic group, for each set of CC subregions. Using the "nearest neighbour classification" rule with Euclidean distance in feature space and two label categories, we computed the label of each of the 40 feature vectors in turn on basis of the known labels of the remaining 39 samples (i.e. "leaving-one-out" classification). For each run of 40 classifications we calculated the empirical error rate as total number of misclassifications divided by sample size.

2.5. CC shape analysis

The differences in CC shape between the dyslexic and the control group were investigated by comparing the prototypes (average shapes) of the CC shapes obtained from the available tracings. We used a method for automatic shape alignment that overcomes the need for manual point correspondences to compute shape prototypes for the two groups. This method is recently described in depth by Duta et al. [33,32] and also shown in Fig. 3.

The shape prototypes for the dyslexic and control group are shown in Fig. 4. The control group prototype is shown in grey and the dyslexic group prototype is shown in black. After aligning the rostrum of the two prototype shapes, a four-pixel length difference was noticed (Fig. 4a). As seen in the figure, there was an almost perfect matching of the rostral and splenial parts of the two CC prototypes, whereas the difference in length seems to be located in the midbody/isthmus region. To test this further, the dyslexic group prototype was cut into two pieces in the midbody region, and the two parts were aligned separately to the normal prototype (Fig. 4b). The location of the cut was determined by allowing the ideal alignment of rostral and splenial parts of the CC between the groups with the following procedure. The matching rostral parts of both prototypes were aligned and the shorter one (dyslexic) was cut at the point where the contours began to differ from the other one (control). The remaining splenial part of the dyslexic prototype was then aligned to the control CC.

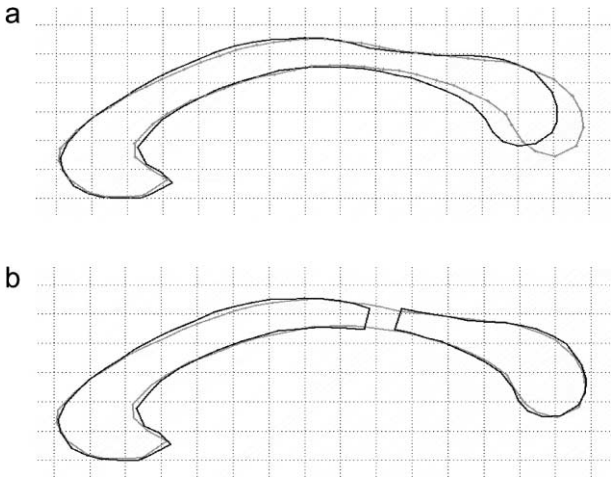


Fig. 4. Comparing the control (shown in grey) and dyslexic (shown in black) average CC shapes (prototypes) (a). The dyslexic prototype is cut into two pieces that are aligned separately at rostrum and splenium (b). The posterior midbody region in the dyslexic subjects is significantly shorter than in the control subjects.

Next, we designed a classification system which, given a CC shape instance, computed the length of the posterior midbody region and assigned it to one of the two groups. Since there were no real anatomical landmarks defining this region, we decided to measure its length with respect to Witelson's division of the CC (see Fig. 1). Two templates representing the anterior half and posterior third of the CC were computed from the control prototype in Fig. 4 by eliminating the remaining part of the midbody region (A5 in Fig. 1). These two templates, shown in black in Fig. 5, were separately aligned to a new shape instance representing in turn each of the 40 subjects in the study. Subsequently, we computed the distance that separates the aligned templates (shown in Fig. 6a for the dyslexic group and in Fig. 6b for the control group).

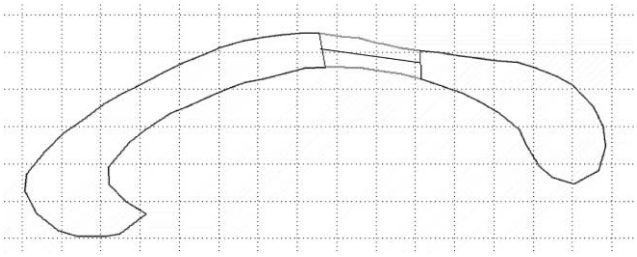
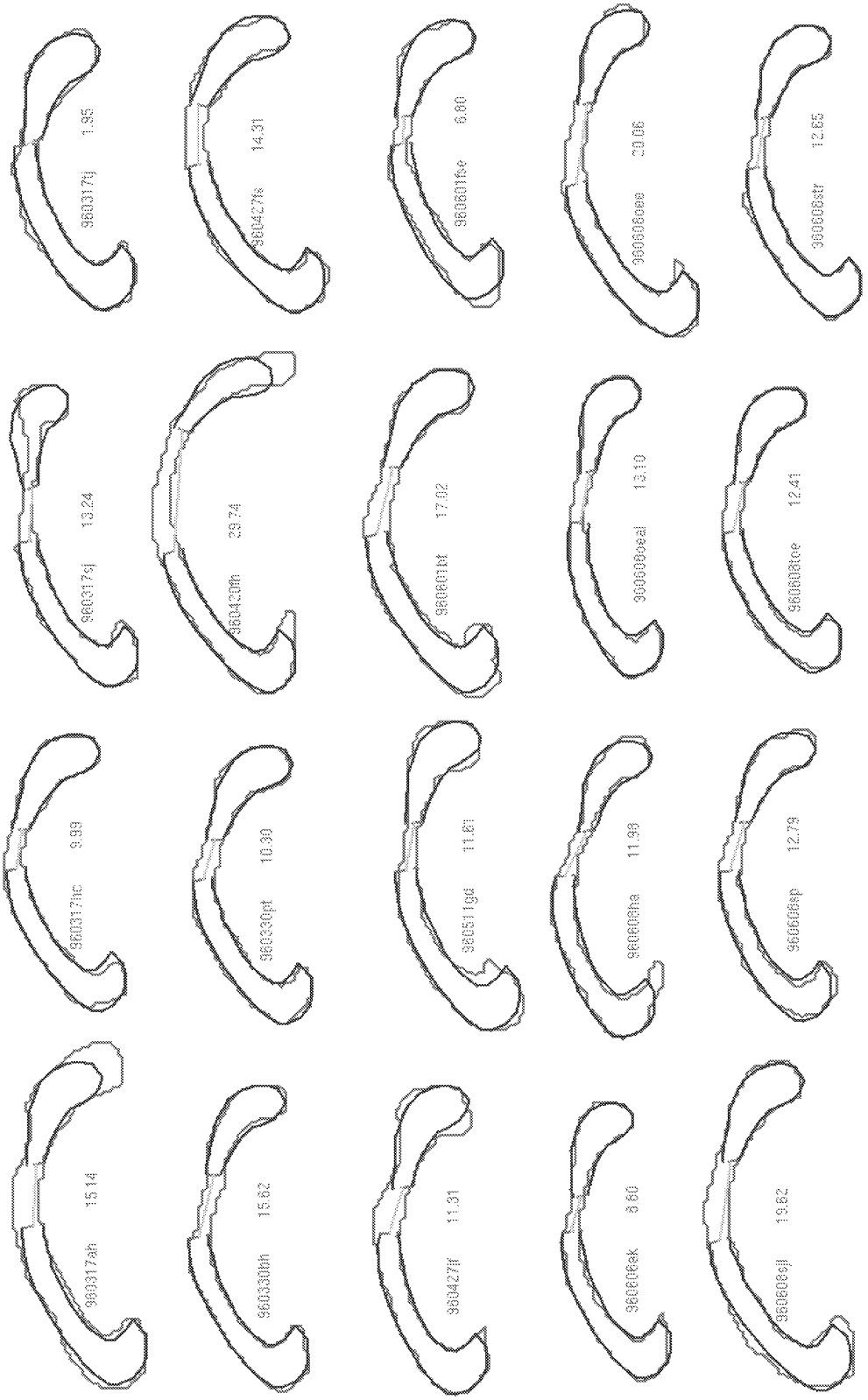


Fig. 5. Two templates representing the anterior half and posterior third from the CC control prototype (see Witelson's subdivision Fig. 1). The segment that lies in between these two templates was measured for classification.

(a)

Fig. 6. Template pieces of the control prototype CC were separately aligned to all CC shapes and the distance between them was measured in the dyslexic group (6a) and the control group (6b).



(b)

Fig. 6. (*Continued*).

Table 2
Mean values (SD) for CC area measurements

	Dyslexic group, n =20 (mm^2)	Control group, n = 20 (mm^2)
Total CC area	662.6 (79.9)	659.85 (99.9)
Midsagittal cortical brain area	10582 (781)	10999 (838)
Anterior third	294.9 (41.9)	288.3 (49.1)
Mid-third	135.2 (20.1)	138.8 (23.7)
Posterior third	225.6 (34.5)	232.9 (38.5)

3. Results

3.1. Area measurements

Inter-rater reliability for the CC perimeter measurement was 0.92. The intra-rater reliability was 0.93 and 0.94.

There were no statistically significant differences between the groups with respect to overall CC area, areas of the seven subregions, thirds, or midsagittal cortical brain areas (see Table 2).

The outcome of the multivariate nearest neighbour classification study confirmed the previous result of no CC area differences between the dyslexic and the control group. No combination of subregion areas (A1, . . . , A7) could discriminate the dyslexic and control group.

3.2. Shape analysis

By computing the two CC prototypes, we found a four pixel length difference between the groups, that was best located at the posterior midbody/isthmus area in shape space.

3.3. Classification

The distributions of the inter-template distances for the 20 dyslexic and 20 control subjects are shown in Fig. 6a and b. The two distributions are well separated though some overlap is present, as shown in Fig. 7. A threshold which minimises the overall error rate was set at a pixel length of 11 and all shapes with an inter-template distance smaller than 11 were classified as dyslexic while the ones with a greater distance were classified as controls. There were nine misclassifications (five controls classified as dyslexic and four dyslexic classified as controls). Thus, 78% of the CC shapes could be accurately classified by this method.

4. Discussion

Using new methods for statistic shape analysis we found reliable differences in the length of the CC in shape space, with a shorter posterior midbody in the dyslexic group. This shape abnormality was confirmed by an automatic classification procedure with an accuracy of 78% over the entire sample. Although this accuracy may not be considered high enough for an “automatic screening tool”, we believe that it provides evidence that the CC midbody shape of dyslexic children actually is shorter. There were no significant group differences for overall CC size.

To our knowledge, the present study is the first attempt to set up a prediction model for dyslexia based on CC shape differences. The model measures the length of the region which remains after removing the anterior half and the posterior third of the CC. Thus, our region of interest lies according to neuro-anatomical conventions in the posterior midbody, the region adjacent to the isthmus. Fibres that are thought to cross over in this area are the sensorimotor ones as well as fibres from the superior and posterior parietal region and from the superior temporal region [9,10,26]. Temporal and parietal lobe regions are crucial for the development of language and language processing, since they contain the primary, secondary and tertiary auditory cortical areas. It is known that the posterior CC undergoes a massive myelination in normal readers during the years of reading acquisition [11]. Our shape analysis indicates that the CC in the dyslexic group fails to undergo this development, which

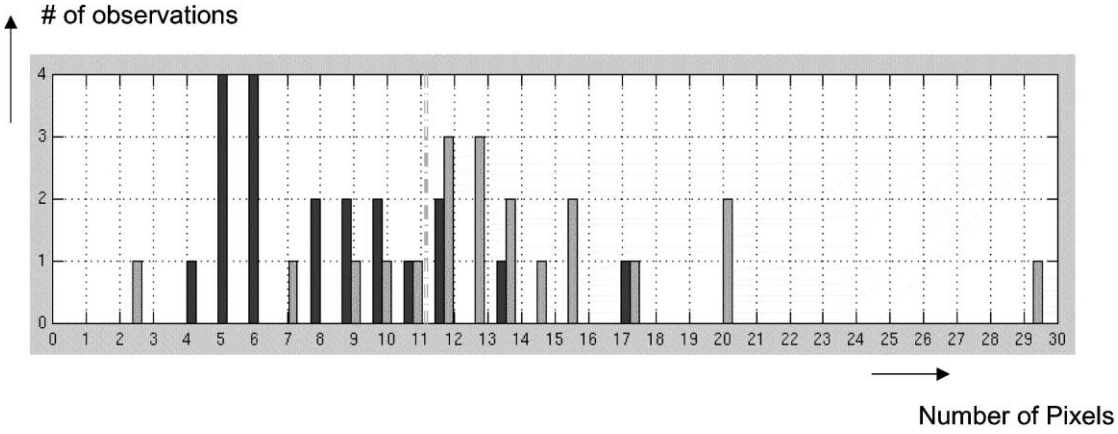


Fig. 7. Distribution of the between-template distances for the control subjects (black) and dyslexic subjects (grey). A threshold was set at a pixel-length of 11 (the vertical segment) and all shapes with a smaller between-template distance were classified as belonging to the dyslexic subjects, while shapes with a greater distance were classified as belonging to the control subjects (78% accuracy).

results in a shorter CC, Castro-Caldas et al. [44], who studied the influence of learning to read and write on the morphology of the CC in illiterate and literate subjects found significant differences in the posterior midbody section with a thinner CC in the illiterate group.

It is important to keep in mind that our method reports characteristics detected by a shape analysis and the difference between the prototypes hence is found in shape space. Concerning our finding of no overall area differences, we found that there were nevertheless inter-individual area differences in both groups (see S.D. in Table 2). It almost seems as if there was a group of individuals with small and others with large CC area within both groups. The spatial distribution of these area differences once more supports a shape analysis as a promising method to look upon the fibre distribution of the CC without solely focusing on area measurements. The fibre distribution and shape of the CC may to a greater extent mirror its development.

In a Procrustes analysis, the data processing also involves rescaling of the CC contours (here not more than 4%) to allow a comparability of the data in shape space. Our main finding detects "latent" morphological features of the CC, which involved mostly length and to a lesser extent also thickness. It thus seems that it is a combination of thickness and length that differentiates the two groups. This finding matches well with the study of Robichon and Habib [19] who reported more curvature of the CC midbody in the dyslexic group. It also fits with the findings of other studies concerning the development of the CC, which have reported a thinning and lengthening of the CC with age. Our findings suggest that this development may be retarded or not taking place at all in dyslexia.

A less developed CC in the dyslexic group may be due to several factors. It could be part of a biological syndrome with a genetically determined deviation in the brain development resulting in an impaired function of the auditory system and subsequently minor growth of the part of the CC containing auditory fibres. This in turn would result in a dysfunction of phonological decoding. From this perspective our findings relate well to a view of dyslexia as due to failure of acoustic discrimination [45,46]. Tallal and coworkers suggested that dyslexia involves impairment of temporal processing of rapid acoustic events. Such impairment could be related to reduced trafficking across the CC midbody/isthmus area in dyslexic individuals.

The areas in the superior temporal gyrus and in the temporo-parietal junction are considered critical for speech understanding and phonological decoding [47]. The planum temporale (PT) area in the superior temporal gyrus is typically larger on the left side in normal readers [48,49]. The results of brain imaging studies of the planum temporale have been inconsistent, perhaps due to diagnostic uncertainty, technical differences, and lack of control of handedness, sex, and cognitive ability. Although structural imaging studies have not fully clarified the neurobiology of reading disability, converging evidence suggests that variation in asymmetry of the planum temporale does have functional significance. Recent studies have found a reduction in PT asymmetry [50] in dyslexic subjects, particularly involving the left PT [34,35]. In further research it would be useful to explore the relationship between PT asymmetry reduction and CC shape in the critical regions.

It has also been shown that CC development is dependent on environmental factors [44,51]. The anterior to posterior myelination of the CC follows exactly the motor development. This means that a developmental abnormality of the posterior midbody of the CC could be a consequence of lacking stimulation due to delayed reading acquisition. Today we cannot decide whether the less developed CC is a cause for or a consequence of developmental dyslexia. [2]

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