

Neurobiology of developmental dyslexia Part 2: A review of magnetic resonance imaging (MRI) studies of the corpus callosum

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Abstract

This paper forms part two of a review of the neurobiology of developmental dyslexia (DD) and here the focus is on magnetic resonance imaging (MRI) of the corpus callosum (CC) of dyslexic and non-dyslexic subjects. The CC is a bundle of nerve fibres connecting the left and the right hemisphere of

the brain. Due to the role of this structure in inter-hemispheric transfer and integration between the hemispheres, the CC is significant in the search for the neurobiological basis of DD. (*S Afr Optom* 2012 71(1) 39-45)

Key Words: Developmental dyslexia, corpus callosum, magnetic resonance imaging (MRI), optometrist and dyslexia.

Introduction

Beside theories and studies associating anatomical deviations in brain structures (asymmetry /symmetry) of the planum temporale (PT) to dyslexia¹⁻³, another proposed mechanism in the neurobiological deviations in dyslexic brain is an abnormal collaboration between the brain hemispheres. The corpus callosum (CC) is a bundle of neural fibres beneath the cortex that connects the left and right cerebral hemispheres⁴⁻⁶ and it is the largest of the three commissures (bundles of nerve fibres that connect the two cerebral hemispheres) of the human brain, consisting of between 200 and 800 million axon fibres⁴⁻⁶. In providing a connection between homologous cortical areas, the CC functions primarily to facilitate inter-hemispheric communication between the two hemispheres and also plays an important role in the development of hemispheric asymmetry, cerebral dominance and laterality⁴⁻⁶.

The CC consists of three main anatomical parts.

The anterior part is called the *genu*, the posterior part is the *splenium*, between the genu and the splenium is the *truncus*, or body of the CC. The part between the body and the splenium is characteristically thinned and thus referred to as the *isthmus*. The *rostrum* is the part of the CC that projects posteriorly and inferiorly from the anterior-most genu^{4-5, 7-8}. The genu contains the highest density of thin myelinated axons whereas the splenium contains thick axons⁴⁻⁵. As the CC provides a connection between homologous cortical areas, the areas of CC has been shown to be “topographically organized with projections from specific cortical areas to specific callosal regions; anterior areas of cortex are connected through more anterior pathways”, likewise for the posterior areas^{4, 9}. In a mid-sagittal cross-section (dividing the body into right and left passing through the midline)^{8, 10}, the macroscopic borders of the CC are not clearly defined, but microscopic techniques reveals myelinated axons with a relatively small diameter in the anterior and posterior third of the CC whereas fibers in the mid-

body and posterior splenium contain thick fibers⁸. The CC is one of the anatomical structures of the human brain that is relatively easy to study *in vivo*^{8, 11-12} and the sections can be subdivided into several functional and morphologically distinct sub-regions based on the topographical organization of cortical areas^{8, 5}. The main classification system used in the study of the CC is the Witelson's which defines five vertical callosal segments derived from dividing the CC along its anterior-posterior dimension and it is based on a general principle that (i) the anterior third of the CC contains fibres connecting the bilateral prefrontal cortices on either hemisphere and higher order sensory area (ii) the anterior and posterior mid-body (middle third) primarily contains crossing fibres for motor, somatosensory, and auditory cortices (iii) the splenium (posterior fifth) carries fibres mainly to temporal, parietal, and occipital lobes and (iv) the isthmus (in between the mid-body and splenium) is thought to carry fibres connecting perisylvian regions^{8, 10}.

The CC mediates its role in inter-hemispheric transfer and integration through either inhibition or excitation of its functions^{4, 13}. The inhibitory function is a passive process and implies that CC performs its role by providing a pathway through which one hemisphere can inhibit the other thereby dominating a given function whereas the callosum's excitatory role in inter-hemispheric processing implies that the CC actively integrates its function of cerebral processing between the two hemispheres. Consequently, an increase in the connectivity between the hemispheres would decrease lateralization due to the excitatory qualities of the CC hemisphere^{4-5, 13}. Both inhibitory and excitatory messages have been demonstrated to pass through the CC⁴.

Apart from the principal role in inter-hemispheric integration, the CC plays an important role in the transmission of visual and auditory information in reading¹⁴. Reading is an acquired skill coordinated by a complex system¹⁵, which depends on the establishment of a facilitating neural circuit¹⁶. During reading, different brain areas are activated and the reading activity requires the flow of information from the posterior lobes to the frontal lobe of the brain^{8, 17}. In particular, word decoding (recognition) relies on the transfer of information between brain hemispheres; the left hemisphere processes information sequentially and specializes in linguistic processing whereas

the right hemisphere (for most right handed persons) processes information in a holistic way and specializes in the identification of visual patterns¹⁸. Reading, a linguistic activity which engages both hemispheres and diverse areas of the brain requires efficient communication between these entities¹⁸. In multi-factorial conditions such as dyslexia, both genetic and environmental factors influence the establishment of this circuit and may result in faulty phonological awareness and a reading disability¹⁶, thus emphasizing the role of the CC in neural circuitry in reading.

The role of the CC in reading disorder has been well-documented in the literature¹⁹⁻²⁷. Temple *et al* (cited by Galaburda)¹⁹ suggested that congenital abnormalities in the CC are associated with reading disorders. More so, it has been demonstrated that defective inter-hemispheric integration and transfer of information is associated with reading disorders²⁰⁻²¹ and that some children with learning disabilities (LD) also display neurological signs suggestive of inter-hemispheric disconnection²². Another perspective is that autopsy studies²³⁻²⁴, as well as neuro-imaging studies²⁵⁻²⁶, have revealed symmetry and an enlargement of the PT, a language-relevant cortical structure in the brain. The presence of enlarged PT associated with symmetrical PT was suggested to be due to reduced cell death during fetal development which then results in an increased number of axons passing through the CC²⁷. The resultant larger callosal area however, precludes a high capacity for inter-hemispheric transfer of information to the perisylvian-language regions due to the presence of ectopias (misplaced neural cells)^{6, 23-24, 27}.

Overall, due to its principal role of inter-hemispheric transmission and integration of information and specifically its role in transmission of visual and auditory information in reading²⁴, the CC has been an area of intense research in the quest for the neurobiological substrate of DD. In this paper, MRI studies of the CC of dyslexic and normal readers are reviewed to address the question of whether anatomical deviations (morphology of the CC in this case) distinguish the dyslexic and non-dyslexic brain.

A review of magnetic resonance imaging of the corpus callosum

Magnetic resonance imaging studies on the CC

have compared the relative size, shape or subdivisions of the CC between dyslexics and control.

Findings on the Genu

Hynd *et al*¹², in 1995, examined the morphology of the corpus callosum in 16 dyslexic (Mean age 116.50 months) and 16 control children (Mean age 132.75 months) matched by gender. Using a midsagittal scan they obtained area measurements for five regions of the CC, although only the results for the genu and splenium were reported. Significant differences between dyslexic and the normal-reading group were found only in the genu, which was smaller in the dyslexic children. The authors also reported a moderate correlation between reading achievement and the relative size of the genu and splenium, which led to the conclusion that successful reading acquisition is associated with a larger CC particularly in the posterior and anterior regions²².

Findings on the Splenium

Two studies²⁸⁻²⁹ reported enlarged spleniums in the dyslexic group. First, Duara *et al*²⁸ measured the area of subdivisions of the CC on a midsagittal brain section, obtained from 21 dyslexic (Mean age 39.1 ± 11.0 years) and 29 control subjects (Mean age 35.3 ± 10.0). Dyslexic subjects had larger spleniums than non-dyslexic subjects, and dyslexic female subjects had larger spleniums than dyslexic male subjects²⁸. Furthermore, both the genu area and the CC in general were found to be larger in female than in male dyslexic adults². Rumsey *et al*²⁹ measured the anterior, middle, and posterior regions of the CC of 21 dyslexic men (Mean age 27 ± 5 years) and 19 control (Mean age 27 ± 6 years). Using the “whole corpus callosum as a covariate”, the authors found that the area of the posterior portion of the CC—roughly corresponding to the splenium and the isthmus was significantly enlarged in dyslexics relative to control subjects (one-tailed $p = 0.01$) and that neither the anterior nor the middle portion of this structure differed between groups.

Findings on the total callosal area

Several studies^{6, 14, 22, 28, 30-31} reported differences in total callosal area or shape/length of the CC but only two^{6, 14} found the CC to be shorter in dyslexics. First, the study by Von Plessen *et al*¹⁴ compared both shape and size of the CC and its sub regions be-

tween 20 right-handed boys with DD matched in age (Mean age 142 months), gender and handedness with 20 right-handed boys (Mean age 141 months) as control. The authors reported that shape analysis revealed shorter CC shape in the dyslexic group, localized in the posterior isthmus region but there were no significant group differences in overall CC area/size or sub-regions¹⁴. This region contains inter-hemispheric fibres from primary and secondary auditory cortices. The authors¹⁴ claimed that the shape abnormality was confirmed by an automatic classification procedure with an accuracy of 78% over the entire sample and that a shape length difference larger than a fixed threshold in the posterior mid-body region could correctly discriminate between control and dyslexic subjects. It was also noted that dyslexics presumably fail to undergo the massive myelination in this region during reading acquisition¹⁴. The second study in 2008 that found shorter CC in dyslexics was reported by Duta *et al*⁶. The authors investigated the extent to which the shape of the CC can predict the presence of dyslexia. Their statistical shape analysis revealed differences in CC on the length of the isthmus region between a group of 20 normal (Mean age 35.3 ± 10.0 years) and 20 dyslexic subjects (Mean age 39.1 ± 11.0 years). The dyslexic CC shapes (in the isthmus) was found to be shorter than normal. Duta *et al*⁶ concluded that their study was the first to attempt to automatically predict dyslexia based on the characteristics of the CC extracted from MR images.

Other studies^{16, 22, 28, 30-31} that reported on the total callosal size found increased sizes of the CC. In 2010, Casanova *et al*¹⁶, using a novel pattern recognition technique that offers a point-by-point shape descriptor of the CC examined 16 dyslexic men (Mean age 28.2 years) and 14 age-matched controls (Mean age 25.1 years). The study revealed a generalized increase in the size of the CC in dyslexia with a concomitant diminution at its rostral and caudal poles. Duara *et al*²⁸ found the CC in general were larger in female than in male dyslexic adults. Njokiktjien *et al*²² studied callosal size in children with LD which included 39 dyslexic (age range was 2.5 to 14 years) and 42 control subjects (age range 0 to 20 years). The authors²² found that children with familial dyslexia, had a thicker CC, which they claimed was an indication of poorly understood neuro-developmental mechanism that inhibits the establishment of cerebral dominance.

Robichon and Habib³⁰ studied CC morphology in 16 dyslexic adults and 12 controls using a high resolution brain MRI scan. The two groups differed remarkably with respect to the shape and regional size of the CC, with the dyslexic subjects exhibiting a more circular and rounded thicker callosal shape than the control subjects³⁰. Secondly, the mid-sagittal surface is on the average larger than in controls, in particular in the isthmus³⁰. Also, Robichon *et al*³¹ in 2000 used a novel method based upon the measurement of four angles, analyzed the CC of 23 adult male dyslexics (24.47±5.68) and 25 age-matched controls (Mean age 26.82 years) on MRI sagittal scans. Two out of the four angles measured showed significant differences between the groups that were consistent with previous findings³⁰ concerning the size of the CC in dyslexics. In particular, posterior regions indicated a lowered situated CC in dyslexics³¹.

Four studies^{29, 32-34} found no difference in total callosal area. First, Pennington *et al*³² in a study that controlled for age, gender, ADH and intelligence quotient, examined brain structure differences in dyslexic and control subjects. The subjects comprised 75 individuals with reading disability (RD) (Mean age 17.43 ± 4.29) and 22 control subjects without RD each a single member of a twin pair. The authors found no difference in any part of the CC between the dyslexic and control group. Cassanova *et al*³³ studied brain size in 16 dyslexics and 14 control. The authors found no differences in the cross-sectional area of the CC in dyslexics and control. Larsen *et al*³⁴ found no differences in the total callosal area or the splenium in male sample of 19 dyslexic adolescents and 17 normal readers. The authors also reported no difference in size of the CC in sub-groups of dyslexia related to reading profile or symmetry. Similarly, Rumsey *et al*²⁹ found no difference in relative CC area.

Discussion

A direct comparison and synthesis of the studies on CC morphology is complicated due to considerable variations in methods (especially characteristic of participants) and diverse findings across studies. Only the study by Hynd *et al*¹² found the genu to be smaller in the dyslexic children. The authors argued that their findings of a reduced genu may be due to the bilateral frontal cytoarchitectonic anomalies found in

the brains of dyslexic individuals. Duara *et al*²⁸ and Rumsey *et al*²⁹ reported the spleniums to be enlarged in the dyslexics compared to controls. Although the studies by Duara *et al*²⁸ and Rumsey *et al*²⁹ reported similar findings of enlarged spleniums in the dyslexic group, both studies used different mid-sagittal slice thickness (Duara *et al*²⁸ = 7 mm, Rumsey *et al*²⁹ = 5 mm) as well as varying gender and age ratios (see table). More so, in the study by Duara *et al*²⁸ co-diagnostic variables such as attention deficit hyperactivity disorder was not controlled. In the discussion of their findings, Rumsey *et al*²⁹ suggested that the increased area of the posterior CC may reflect anatomical variations associated with deficient lateralization of function in posterior language regions of the cortex. The splenium which comprises part of the posterior third of the CC contain fibres from the temporal and posterior parietal cortex, as well as from occipital cortex^{4, 8, 10}. Specifically, the splenium may be considered the most critical region because it contains axons linking the PT and the angular gyrus³⁵. Also, as the reading process is a complex task that relies on the brain systems in the posterior, parieto-temporal, and occipital brain regions in the left hemisphere³⁶, the findings of enlarged spleniums therefore may be relevant to the etiology of dyslexia as this region contains fibres from the temporal and posterior parietal cortex, as well as from occipital cortex which is associated with posterior language regions^{29, 36-37} the same region where unusual anatomical asymmetries have been reported in magnetic resonance imaging^{28-29, 34, 38}.

Duta *et al*⁶ and Von Plessen *et al*¹⁴ found shorter CC although there are also some differences in the subjects' characteristics between the two studies. As the posterior CC undergoes a massive myelination in normal readers during the years of reading acquisition¹⁴, Von Plessen *et al*¹⁴ suggested that in their study, shape analysis indicates that the CC in the dyslexic group fails to undergo that development, which then resulted in a shorter CC, a finding which they argued, corroborates the findings of Castro-Caldas *et al*³⁹ who studied the influence of learning to read and write on the morphology of the CC in illiterate and literate subjects and found significant differences in the posterior mid-body section with a thinner CC in the illiterate group. Thus, Von Plessen *et al*¹⁴ suggested that fibres that are thought to cross over their measured region of interests in the posterior mid-body, the

region adjacent to the isthmus area are the sensorimotor ones as well as fibres from the superior and posterior parietal region and from the superior temporal region. 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 areas¹⁴.

Three studies^{16, 28, 30} found larger CC in the dyslexic population. Also, there are some methodological variations among the studies. Overall, enlarged CC may suggest that the CC of dyslexics have failed to undergo the usual developmental evolution that normally gives the typical shape of the CC³⁰. This shaping process presumably occurs during the peri-natal period and the first post-gestational weeks and would result from conspicuous loss of axons during this critical period. Subsequently, the callosal area will increase gradually to adulthood, probably reflecting the progressive myelination of persisting fibres³⁰ which then implies that larger CC in dyslexics would reflect incomplete expression of these regressive events³⁰. However, the finding of smaller CC in some dyslexic brains¹² is not consistent with this hypothesis. An enlarged CC could also result from some hereditary brain mechanisms²². In addition, a large CC might develop prenatally if cell death does not occur and if an excess of callosal neurons cross the midline²².

Taken together, the contradictory findings in the MRI results on the CC may be due to some methodological differences. Specifically, methodological variations in CC studies may be due to the following factors:

- effect of subjects placement within the scanner and differences in the orientation of the scan plane used to generate the mid-sagittal image may result in variability in appearance and area measurements of the callosum⁴⁰⁻⁴¹
- difficulty determining a proper mid-sagittal section^{6, 11}
- the possible influence of the brain volume on estimated CC area as well as differences in methods for segmentation and subdivision of the CC⁶
- inadequate control for independent variables such as gender, brain size, socioeconomic status, cognitive variables, handedness, age and diagnosis¹¹
- the methods for subdivision of the CC have also

differed between studies. Some studies on CC morphology relied on Witelson's classification of 1989^{5, 8} whereas a marked difference were reported by Hofer⁸ in the mid-body and anterior third of the CC. In particular, callosal motor fibres bundles were found to cross the CC in a more posterior location than previously indicated⁶. Therefore, it is unreliable to compare results directly when methods for subdivisions are different.

In addition to variables associated with differences in methodologies, other factors which may contribute to differences in CC measurements across studies are: Firstly, the CC is the main axonal pathway in the brain but there are additional commissures in the brain. The functions of these sub-cortical commissures may be confounding in these studies on the CC morphology and its role in inter-hemispheric transfer of information⁴. In addition, brain morphology is influenced by genetic and environmental factors^{14, 39, 42} resulting in an impaired growth and function of the part of the CC containing auditory fibres which would result in a dysfunction of phonological decoding^{14, 42}. Environmental factors that may affect the developmental abnormality of the posterior mid-body of the CC could arise from lacking stimulation due to delayed reading acquisition^{14, 39, 42}.

From a neuro-developmental point of view, differences in callosal size may reflect hormonal influences during critical periods of development of inter-hemispheric connections⁴³. Specifically, testosterone has been considered an etiological factor in CC development and may influence callosal morphology by altering naturally occurring neural regressive events in the perisylvian regions of the neocortex⁴⁴. Low levels of testosterone has been hypothesized to reduce axon elimination, resulting in a larger isthmus of the CC and a subsequent reduction in functional brain asymmetry and laterization, a hypothesis supported by evidence including findings of gender and handedness differences in CC morphology⁴⁵ and by the observation that the CC may be larger in homosexual males in whom lower than normal androgen levels during early development have been hypothesized⁴⁴. Furthermore, callosal transmission may be affected by defects in the fibres of the CC as well as by anomalies in the cells in the region of origin^{12, 20}. Also, size variations

in the CC may reflect differences in the number or size of axons that connect these regions, an increase in extra-cellular and vascular space. Changes may also indicate differences in the number of cortical neurons within homologous regions^{12, 20}. Invariably, an abnormally thick CC would inhibit right hemisphere competence and impair reading^{22, 44, 46-48}.

Summary, conclusion and recommendations

The review of studies comparing the CC of dyslexic and normal readers yield contradictory results. In summary, eleven studies have measured *in vivo* the size or shape of the corpus callosum in dyslexic participants compared to control group. One study¹² found smaller genu in dyslexics, two studies²⁸⁻²⁹ reported enlarged splenium in dyslexics and two studies^{6, 14} reported shorter CC in dyslexics. Also, five studies^{16, 22, 28, 30-31} reported increase in the size of the CC in the dyslexics whereas three studies³²⁻³⁴ found no difference in callosal size between dyslexic and control.

In conclusion, although some studies found a difference in the morphology of the CC between dyslexic and control, there is no consistent evidence to fully establish a link between CC morphology and dyslexia. The main limitation with studies on CC morphology is the lack of consensus on the methodological approach. Therefore, more research, possibly collaborative research from different laboratories, among experts is needed so that documented sources of variations can be controlled. This approach will better clarify whether there are differences in CC morphology between dyslexic and normal readers. Specifically, studies should be designed to simultaneously examine the effects of independent variables such as gender, brain size, socioeconomic status, cognitive variables, handedness, age and diagnosis¹¹. In addition, measurement techniques should be simple enough to allow rapid collection of data in many subjects considering that studies of biological factors influencing human brain structure require large samples^{7, 11}. Finally, although the CC is the main axonal pathway connecting both hemisphere of the brain⁴, it will be necessary to consider the roles of sub-cortical commissures in inter-hemispheric transfer.

This review is intended to enhance our understanding of the neurobiology of developmental dyslexia.

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