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Original Contribution

Callosal Morphology Concurs With Neurobehavioral and Neuropathological Findings in Two Neurodevelopmental Disorders

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• To integrate neuroimaging, neuropathologic, and neuropsychological findings, computer-assisted morphometry was applied to magnetic resonance images of the corpus callosum in adolescents with Down and Williams syndromes and in control subjects. Callosa of subjects with Down syndrome were distinctively rounded in form, consistent with Down syndrome brachycephaly. These callosa also showed decreased widths throughout their rostral fifth, which serves frontal lobe projections. This finding correlates with the hypocellularity and hypofrontality of neocortex in subjects with Down syndrome and with their neuropsychological profile of frontal lobe dysfunction. Callosa of subjects with Williams syndrome generally resembled control specimens, in congruence with their frontal lobe structure and better preserved frontal lobe function. These results represent a convergence of findings across levels of neuroscientific investigation.

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Previous studies of the structure of the corpus callosum (CC) usually have provided global descriptions, reporting such variables as length (from the most rostral to the most caudal point), height, total cross-sectional area, and general conformation. Only a handful of imaging studies have made regional callosal measures beside width determination at arbitrary points along the CC and various measures of splenial structure (which is argued to be sexually dimorphic).[1-8] A related point is that even fewer pathologic studies have addressed the topography of the CC, despite its obvious importance.[9-11]

There also has been a dearth of studies on the CC in genetic syndromes of cognitive impairment. However, Down syndrome (DS), the most frequent genetic cause of mental retardation, has been extensively subject to other neuropathologic study. The most prominent anomalies of gross structure in DS include simplicity of the convolutional pattern, narrowness of the superior temporal gyrus, conspicuous smallness of the cerebellum, and an unusual foreshortening of the cerebrum due to frontal lobe hypoplasia.[12-17] Histologically, many investigators have reported decreased cellular density in the DS cortex, including layers II and III. (See Coyle et al[12] for a review.) Since these layers give rise to CC projections, hypoplasia of the CC should not be surprising. In fact, a case of CC hypoplasia in DS has been reported, but without further details.[18]

Williams syndrome (WS) is a second syndrome of cognitive impairment, of probable genetic etiology.[19] (Williams syndrome is medically defined by its facies, including stellate irises, medial eyebrow flare, long philtrum, full lips, malar flattening, and upturned nose with low nasal bridge; frequent supravalvar aortic stenosis and peripheral pulmonic stenosis; frequent hypercalcemia in infancy; and dental, renal, skeletal, and other anomalies.[20-22]) Our laboratory is engaged in a program of studies designed to investigate the unusual neuropsychological profile of subjects with WS in contrast to age- and IQ-matched subjects with DS. We have found that adolescents with WS show significantly better abilities on a variety of linguistic tasks as well as in spontaneous language.[23,24] They also display remarkable abilities in facial recognition and on measures of linguistic affect.[23,25] On visuospatial tasks, where subjects with DS are generally better, adolescents with WS show marked peaks and valleys of ability.[23,26,27]

As part of a large, multidisciplinary study of the neurobiologic bases of language development, Jernigan and Bellugi[28] obtained magnetic resonance studies on these two contrasting groups. Employing computer-assisted voluming procedures developed by Jernigan, they found comparable reductions of cerebral volume in DS and WS but with clear morphologic differences between the two groups. Whereas the scans of subjects with DS showed a brachycephalic appearance consistent with the aforementioned hypofrontality, the scans of subjects with WS tended toward dolichocephaly. In addition, subjects with WS showed preservation of the cerebellum as a whole and the neocerebellar lobules of the vermis in particular. This vermal pattern is opposite to that found in autism, where neocerebellar lobules VI and VII are hypoplastic.[28,29]

Herein we report the results of global and regional analysis of CC structure in the same group of subjects with WS and DS. Such regional analysis allows us to compare the structure of the CC with the known neuroanatomic findings and the well-established neuropsychological profiles of subjects with DS and WS.

SUBJECTS AND METHODS

We analyzed magnetic resonance images that had been obtained by Jernigan and Bellugi[28] and collaborators as part of a large, multidisciplinary study of the neurobiologic bases of language development. Of the eight subjects with DS and 11 with WS recruited, one with DS lacked a technically adequate midsagittal scan. Of those remaining, the DS group (two males, five females) ranged in age from 10 to 20 years, and the WS group (five males, six females) ranged in age from 10 to 20 years. No significant differences were noted in age or IQ between the groups. The diagnoses of DS and WS had been established by medical exam-

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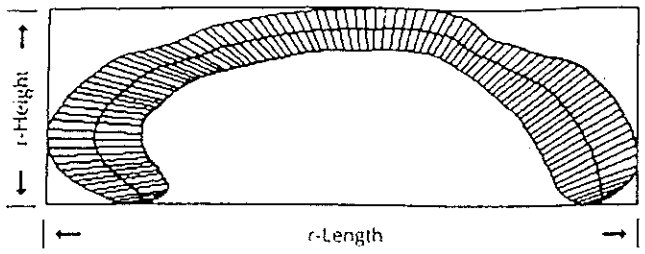

Fig 1.—*Fully processed tracing, using Stereology software, of a control subject's corpus callosum. The perimeter, 99 widths, center line, rectangle length (r-length), and r-height are all illustrated.*

Table 1.—Reliability of Corpus Callosum Measurements*

Measures	r
Global	
Area	.990
r-Length	.992
r-Height	.991
Circularity	.987
Perimeter	.994
Center length	.981
Sum of all widths	.977
Regional: sum of widths	
1-19	.957
20-39	.879
40-59	.944
60-79	.928
80-99	.963

*For explanation of measures, see text. Interrater reliability values were computed by analysis of variance across five repeated measures.

ination and by karyotype analysis for the children with DS. We also analyzed scans from 17 age-matched normal control subjects previously recruited by Jernigan and collaborators.[30] Sixteen of them had served as controls for studies on language/learning impairment, and one had been recruited for studies of psychiatric disorders. All controls were screened with medical and social histories. The first 16 also underwent extensive language and cognitive testing. From the entire set of subjects, we were able to match five individually from each of the three groups based on age and sex. These subjects with DS and WS also matched on full-scale IQ. Informed consent was obtained from all subjects and from their parents (for subjects with DS and WS and for nonadult controls) after full explanation of the procedures involved.

We obtained T_1-weighted midline sagittal images with a General Electric Signa scanner, under a 1.5-T field, at the University of California, San Diego/AMI Magnetic Resonance Institute. A 256×256 matrix and 24-cm field of view were used to obtain 5-mm-thick slices. The specific imaging protocol has been presented previously.[28] All scans were coded for "blind" analysis.

The CCs from the original digitized images were magnified by a factor of 8, using an image-processing program (NIH Image 1.19). Images were then laser printed at a resolution of 300 dots per inch. Thus, the CCs were studied at a magnification of 3.02 times life size. Images were then traced on a Kurta IS/ADB digitizing tablet, using Penworks software, after appropriate calibration. The magnification used was the largest that fit on the digitizing tablet. Morphometric analyses were carried out on a Macintosh SE/30, with Stereology software (KSS Scientific Consultants, Magna, Utah).

As described by Denenberg et al,[31] Stereology computes a perimeter, area, and several other measures for each tracing. An operator designates rostral and splenial terminal points for the CC, thus defining caudal and ventral surfaces. Each surface is then marked at its percentile points. Corresponding caudal and ventral points are connected, giving the 99 callosal widths. The designated terminal points are then repositioned as necessary to minimize the sum of the 99 widths, yielding a more intuitive "fan-shape" to the 99 widths. The midpoints of the 99 widths are connected to form the center line of the CC. Finally, the program draws a rectangle, based on the lowest points of the genu and splenium, that encloses the CC. The length and height of this rectangle are determined (r-length and r-height), and their ratio is calculated. This ratio is referred to as the "circularity."[8,31,32] In addition, we studied five regions of the CC, demarcated by the 20th, 40th, 60th, and 80th width lines. The sum of all 20 widths in each region was computed. For each CC, the entire tracing and analysis procedure was repeated five times by a single experimenter. An example of a completely processed image is given in Fig 1.

Two-tailed nonparametric statistical analyses were performed using StatView 512+ for the Macintosh. The Kruskal-Wallis analysis of variance by rank was employed for three-group comparisons across all subjects. Post hoc comparisons between two groups were made by the Mann-Whitney *U* test. For the matched groups, the Friedman two-way analysis of variance by rank was carried out.

RESULTS

Reliability

Intrarater reliability was calculated for each of the parameters measured. These included the "global parameters": area, r-length, r-height, circularity, center length, perimeter, and the sum of all 99 widths, as well as the "regional parameters": the summed widths in each of the five regions. Results are given in Table 1. As the results show, the procedure employed was extremely reliable. Of the parameters generated directly by Stereology, the lowest reliability for a single determination was $r = .977$. The regional parameters also were highly reliable. Subsequent statistical analyses used the mean of five determinations for each parameter.

Global Morphology

Full clinical interpretations of the scans have been reported elsewhere.[28] Despite the distinct, syndromic profiles of cerebral structure discussed above, no abnormalities of the CC were reported for any of the scans.

Results for the global parameters are given in Table 2. Although no significant differences were found in area, the means were smaller in the DS and WS groups, in comparison with controls. In subjects with WS, r-length (length of the enclosing rectangle), center length, and perimeter were all significantly shorter than control. However, the circularity was no different in subjects with WS than in the controls. These results suggest a smaller but similarly shaped CC in subjects with WS.

In subjects with DS, the trend toward smaller cross-sectional area was reflected in shorter r-length. However, the CC of subjects with DS did not differ in mean height, center length, or perimeter. A qualitative difference in the shape of the DS callosa thus emerged: they were significantly more rounded than either WS or control corpora. This difference can be seen in Fig 2, which shows typical images from patients with DS and WS. Quantitatively, this distinction is reflected in the circularity parameter (r-length/r-height; $P < .001$ overall, $P < .002$ vs both WS and control). The DS and WS groups did not overlap at all on circularity (Fig 3).

Regional Structure

A profile of all 99 widths, from genu to splenium, is given in Fig 4 for all three study populations. The figure suggests that the CC in subjects with DS was thinner ros-

Table 2.—Global Morphology of Corpus Callosum

Measure, Mean ± SD	Down Syndrome	Williams Syndrome	Control
Area, mm²	589±79.6	563±81.0	609±131
r-Length, mm*	65.6±4.24†	69.0±2.42‡	73.2±5.22
r-Height, mm	25.3±2.83	21.8±1.50	23.6±2.89
Circularity*	2.60±0.167†§	3.18±0.235	3.14±0.374
Perimeter, mm	197±15.7	185±6.64†	200±14.9
Center length, mm	89.3±7.34	81.4±3.18†	87.3±6.67
Sum of all widths, mm	726±77.5	754±79.6	758±115

*P < .001, Kruskal-Wallis analysis of variance, among all three groups.
†P < .002, Mann-Whitney U vs control.
‡P < .02, Mann-Whitney U vs control.
§P < .002, Mann-Whitney U vs Williams syndrome.
P < .01, Kruskal-Wallis analysis of variance, among all three groups.

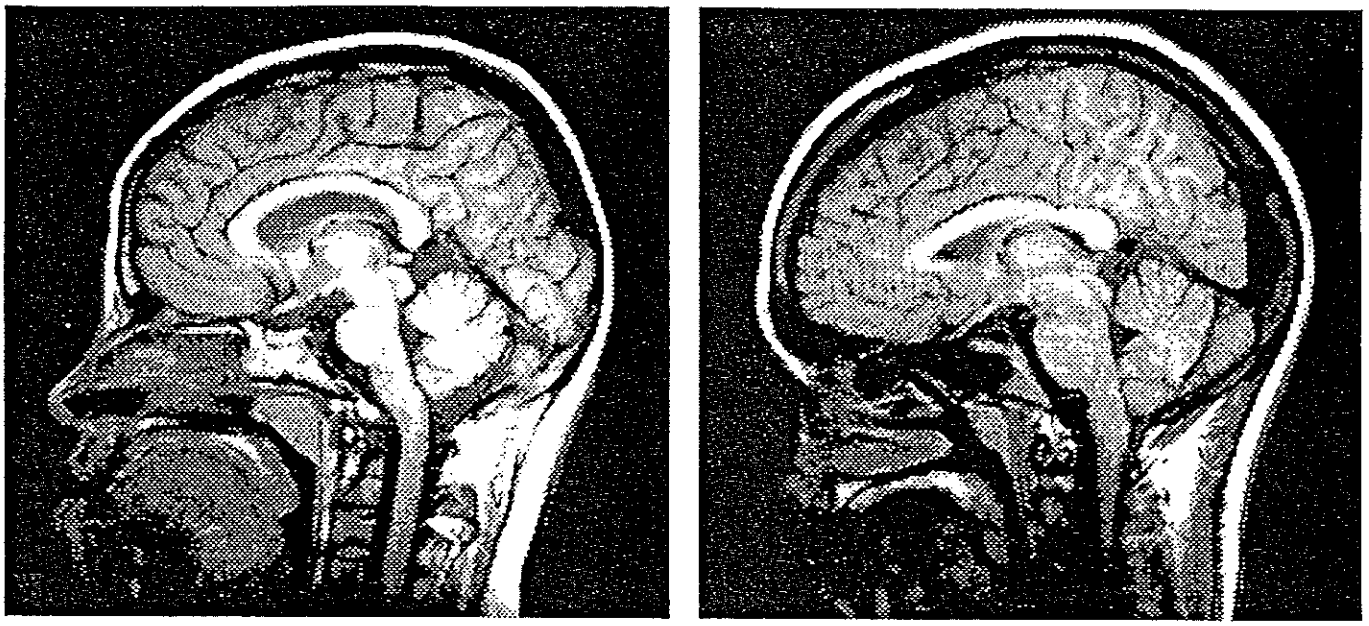

Fig 2.—*Midsagittal magnetic resonance images in Down syndrome (left) and Williams syndrome (right). Note the relative callosal circularity and cerebral hypofrontality of the Down syndrome image.*

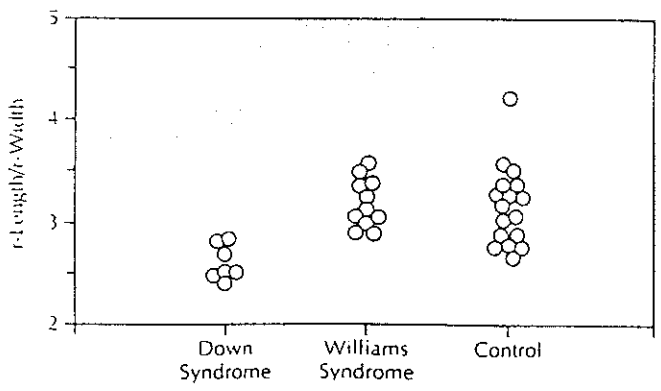

Fig 3.—*Scatter plot of the circularity ratio (ratio of rectangle length to width [r-length/r-height]) for callosa from each group. The Williams and Down syndrome ratios show no overlap.*

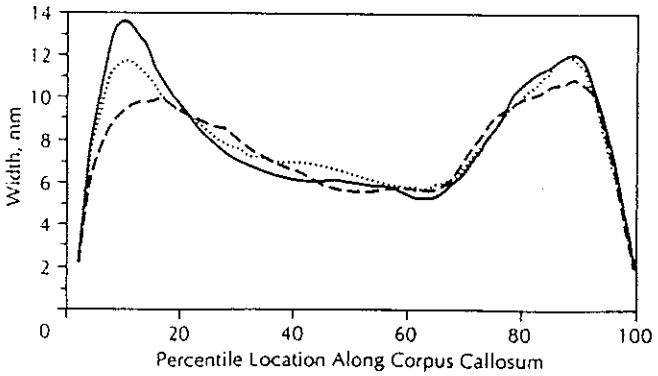

Fig 4.—*Profile of the 99 callosal widths in each group. In the most anterior fifth of the callosum, the sum of the widths is smaller in subjects with Down syndrome (dashes) than among controls (solid line). Dotted line indicates subjects with Williams syndrome.*

trally than in either subjects with WS or control subjects. Statistical analysis bore out this impression for the sum of the first 20 widths ($P<.01$ among all three groups, $P<.002$ DS vs control; the DS vs WS and control vs WS comparisons approached but did not reach significance). Because the total sum of 99 widths was slightly less in subjects with DS than among controls, it seemed possible that the regional finding might just have reflected a global disparity. Therefore, we analyzed the sum of the first 20 widths as a proportion of the sum of all 99 widths. This analysis confirmed that the first 20 widths are shorter in subjects with DS ($P<.01$ overall, $P<.002$ DS vs control). No other portion of the CC was significantly different among the three groups.

A second analysis of the rostral CC was made, utilizing Denenberg's statistical topography of the human CC.[8] In a factor analysis of 104 human CCs, he found that the 99 widths clustered into seven groups. The first of these groups comprised widths 3 through 18. Comparison of these widths among DS, WS, and control groups mirrored the findings for widths 1 through 19.

The global and regional analyses were repeated for the five subjects from each group who were individually matched. The same pattern of differences was found. The circularity was again different in subjects with DS ($P<.05$ overall), and the first 20 widths of the callosum were shorter both absolutely and proportionally ($P<.01$ overall).

Sex Factors

Sex-related differences in CC structure are the subject of controversy. The argument for such differences is probably strongest for total CC area, and for the areas of the genu and splenium.[5,6,33] Also, Denenberg et al[8] found that the CC is more circular in adult women than adult men. Therefore, we repeated these four analyses on our female subjects only (the number of male subjects was too small for statistically powerful analysis). Total area and widths 80 through 99 (corresponding to the splenium) still revealed no effect among the three groups. The first 20 widths did still show an effect, at the $P<.05$ level among all three groups, with DS less than control at $P=.02$. On circularity, female subjects with DS were significantly different as well ($P<.01$ overall, $P=.002$ vs both subjects with WS and controls).

COMMENT

The callosal findings elucidated herein demonstrate that the hypoplasia of frontal cortex in DS is manifest in the interhemispheric projection system. These findings contribute to a coherent pattern of frontal lobe disease in DS. We consider, first, some technical issues in relation to this study, and then proceed to the convergent neuropathologic and neuropsychological findings in DS.

Denenberg et al[8,31] have discussed the Stereology method at length. In comparison with planimetry and hand measurements, its validity for global measures is good. We add a demonstration of excellent intrarater reliability for the method employed.

Our regional measures also compare closely with the few regional measures that have been reported in the literature. For example, the proportional size of the posterior fifth of the CC averaged 24.1% ± 1.9% in our control population, vs 24.6% (right hemisphere speech-dominant) to 29.5% (bilateral dominance) in the report of O'Kusky et al,[1] and 25.6% (male) to 27.9% (female) in the postmortem series of Clarke et al.[5] Some differences might be related to the fact that this study measured the proportion of the last 20 widths to the sum of all widths, whereas Clarke et al measured cross-sectional areas. While these should be closely correlated, the match may not be exact. Witelson[6] and Hynd et al[7] also examined regional areas, but they employed vertical divisions rather than divisions based on the curved callosal profile.

In the same article, Witelson[6] argues strongly for the importance of a sex and handedness interaction in determining callosal structure. Due to the paucity of consistently right-handed subjects with WS and DS, however, we could not address this question statistically. As shown above, though, our female subjects showed the same effects as did the whole groups.

The neuropathological framework for DS and WS was discussed earlier. As stated then, there are syndromic patterns of gross cerebral anatomy: brachycephaly in DS and dolichocephaly in WS. These hemispheric patterns match well with the global callosal geometry found herein: more circular in DS and elongated in WS. Figure 2 shows DS and WS callosa in their matching hemispheric contexts.

Also, regional analyses of the CC showed that its anterior portion was more narrow in subjects with DS than in those with WS or among controls. The validity of this finding is supported by internal and external checks: the findings held true on an absolute basis and as a proportion of the whole CC, and also when repeated with Denenberg's cluster of widths 3 through 18. It is an important result because the anterior portion of the CC serves frontal lobe projections. In humans, this rostral fifth of the CC demonstrates wallerian degeneration in the setting of focal lesions of the inferior frontal lobe.[10] In the macaque monkey, the same portion of the CC shows autoradiographic staining when discrete sectors of the prefrontal cortex are injected with radiolabeled amino acids.[9]

This callosal narrowing does not represent a common dysgenesis. Barkovich and Norman[34] pointed out that dysgenesis of the CC occurs caudally because it results from interruption of the normal developmental sequence, which proceeds from genu to splenium. (An exception is that the rostrum develops last.) Rather, hypoplasia must result from an insult to the cortex or white matter after 18 to 20 weeks of gestation, when formation of the CC is completed. This is consistent with the finding of Schmidt-Sidor et al[16] that frontal lobe hypoplasia in DS is not found until after the 22nd week of gestation. Thus, the frontal lobe hypoplasia of DS is echoed in one of its major projection systems.

Behaviorally, the subjects with DS of this study are deficient on a number of tasks thought to reflect frontal lobe function. Relative to age- and IQ-matched subjects with WS, these deficits include poor verbal fluency, a tendency toward perseveration on a test of verbal memory, and greater difficulty on tasks requiring flexible problem-solving strategy (S.D., U.B., and Dean Delis, PhD, unpublished data, June 1991). Furthermore, abnormalities in event-related potentials have been reported over the frontal cortex in DS, across a wide age range. These include abnormalities elicited by novel stimuli in the context of repetitive background stimuli.[35,36] Such results also are congruent with findings of deviant habituation behavior in DS (as reviewed by Wagner et al[37]).

The specific function of the anterior callosum is less clearly defined. Commissurotomy studies have sug-

gested that it may be involved in the transfer of semantic information.[38,39] This hypothesis would be consistent with the poor semantic fluency of subjects with DS (see above). Additionally, Hynd et al[7] have reported that the cross-sectional area of the genu is smaller in children with attention deficit–hyperactivity disorder. He suggests that this is consistent with the behavioral suggestion of deficient frontal systems in attention deficit–hyperactivity disorder.

No regional differences in structure were found for the WS group in comparison with controls. In comparison with the DS group, the subjects with WS showed relative preservation of the rostral fifth of the CC. This is consistent with the contrast that our laboratory has demonstrated between subjects with WS and DS in frontal lobe volume and on tasks that reflect frontal lobe function.[35,28,40]

Witelson and Kigar[41] suggested that study of the regional structure of the CC might prove fruitful in relation to neuropsychological issues and in relation to the developmental study of cortical regions. We note that studies of the callosum in genetically defined patient groups can contribute also to the understanding of brain-behavior relationships.

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