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BACKGROUND AND PURPOSE: **Regional cerebral blood flow fluctuates synchronously in corresponding brain regions between the hemispheres. This synchrony implies neuronal connections between brain regions. The synchrony of blood flow changes is defined operationally as functional connectivity. Our purpose was to measure functional connectivity in patients with corpus callosal agenesis, in whom the interhemispheric connectivity is hypothetically diminished.**

METHODS: **In three patients with agenesis of the corpus callosum, functional MR imaging was performed while patients performed text-listening and finger-tapping tasks. Functional images were also acquired while the patients performed no specific task (resting state). Regions of activation temporally correlated with the performance of the tasks were identified by cross-correlating the task data with a reference function. Voxel clusters (seed voxels) that corresponded to regions of activation in the task-activation data set were selected in the resting data set. All the voxels in the resting 3D data set that had a correlation coefficient exceeding 0.4 were identified. The number of these voxels in the ipsilateral and contralateral hemispheres was tabulated.**

RESULTS: **In all patients, technically adequate functional MR and functional connectivity MR maps were obtained. For both tasks, activation was found in both hemispheres. For all of the seed voxels, significantly more functionally connected voxels were found in the ipsilateral hemisphere than in the contralateral hemisphere. For most seed voxels, no functionally connected voxels were found in the contralateral hemisphere.**

CONCLUSION: **Interhemispheric functional connectivity in the motor and auditory cortices is diminished in patients with agenesis of the corpus callosum compared with that of healthy subjects.**

In the normal mammalian brain, blood flow fluctuates cyclically, with about four cycles per minute. In functionally connected regions of brain, the blood flow fluctuates synchronously (1–5). For example, blood flow in the left and right motor cortices demonstrates marked synchrony (2). Synchronous blood flow changes have also been noted in the left and right visual cortices, in the thalamus, and in the hippocampus (6). This synchrony implies neuronal connections between these regions. The strength of these connections, the functional connectivity, is defined operationally in terms of the synchrony of the blood flow.

Initial reports suggest that functionally connected voxels are nearly equally divided between hemispheres in healthy subjects. Images in published reports show that comparable numbers of voxels in both hemispheres are functionally connected to a seed voxel in the sensorimotor or auditory cortex. Biswal et al (1) calculated an index for the number of functionally connected voxels in the hemispheres ipsilateral and contralateral to a seed voxel in the sensorimotor cortex (average n_{LL}/n_L and average n_{LR}/n_L) and showed that the difference between them was not significant.

Agenesis of the corpus callosum eliminates a major mechanism for interhemispheric connectivity. The purpose of this study was to test the hypothesis that defects in the corpus callosum substantially diminish the number of voxels functionally connected to a voxel in the contralateral hemisphere.

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Methods

Three patients with agenesis of the corpus callosum, as documented on imaging studies, and without neurologic deficits were selected for the study. Patient 1 was a 58-year-old ambidextrous man with seizures. He had a relatively normal developmental history, walking at age 1 year and graduating from high school, and he was working as a small-engine mechanic. Findings from his neurologic examination were within normal limits. He had mild bitemporal slowing, as shown by EEG. MR imaging showed complete agenesis of the corpus callosum, prominent ventricles, and colpocephaly. No heterotopia or cortical dysplasia was observed. Patient 2 was a 35-year-old unmarried male manual laborer. In this patient, agenesis of the corpus callosum was demonstrated as an incidental finding on CT scans obtained for the evaluation of sinusitis. MR images confirmed the absence of the corpus callosum and showed a small interhemispheric cyst. Patient 3 was a 20-year-old married male electrician who underwent a shunt procedure for hydrocephalus in 1991. At that time, agenesis of the corpus callosum was identified on images. MR images revealed an absent corpus callosum, associated colpocephaly, and an interhemispheric cyst.

Functional imaging was performed by using a 1.5-T commercial imager (Signa; General Electric Medical Systems, Milwaukee, WI) equipped with high-speed gradients. Preliminary anatomic images were obtained with multisection spin-echo sequences. For functional MR and functional connectivity MR examination, images were acquired in the coronal, axial, or sagittal planes as prescribed by the radiologist supervising the clinical imaging study. Whole-brain images were acquired every other second for 270 seconds. Technical parameters for these images included the following: 18 sections, matrix of 64 × 64, 90° flip angle, TR/TE of 2000/50, field of view of 24 cm, section thickness of 7 mm, and gap of 2 mm. Each subject passively listened to text to activate the auditory cortex and performed intermittent bilateral finger tapping to activate the sensorimotor cortex. The tasks were performed in an on-off block-type paradigm with four 20-second epochs of task interspersed with five 20-second epochs of rest. For passive listening to text, a taped narration of a story was delivered to the patient during the task. For finger tapping, the subject was instructed to tap each of the fingers successively to the thumb on both hands. Data were acquired in a similar manner while the patient was resting; that is, while he or she was performing no specific cognitive task. Resting MR imaging was performed immediately after the functional MR examination. The subject was instructed to keep his eyes closed, to imagine a blank screen, and to refrain from cognitive activity as much as possible during the resting scan.

For the images obtained in both the task activation and the resting fMR examinations, signal intensity was plotted as a function of time for each voxel. In both the task and the resting time course data, a three-point Hanning filter was applied for temporal smoothing of the signal intensity. Signal intensities in each section were time-corrected by shifting the smoothing filter corresponding to the temporal offset. A band reject filter was not required for the small effect of aliasing of the cardiac frequency. A Hamming filter applied to the echo-planar raw data in the spatial frequency domain provided a first low-pass filter to increase the signal-to-noise ratio (5).

For functional MR imaging, a least-squares fitting algorithm was used to compare the observed data voxel by voxel to a box

TABLE: Number of Functionally Connected Voxels in Each Hemisphere for a Seed Voxel in One Hemisphere in the Sensorimotor or Auditory Cortex

A: Pattern of functionally connected voxels in sensorimotor cortex

Patient and Seed Voxel Cluster	Seed Voxel in L Hemisphere: No. of Voxels in the LH	Seed Voxel in L Hemisphere: No. of Voxels in the RH	Seed Voxel in R Hemisphere: No. of Voxels in the LH	Seed Voxel in R Hemisphere: No. of Voxels in the RH
A				
1	5	0	0	6
2	6	0	NA	NA
3	8	0	NA	NA
4	10	0	NA	NA
B				
1	7	0	0	12
2	8	0	0	14
3	6	0	0	6
4	10	0	7	17
5	19	7	NA	NA
C				
1	8	0	2	5
2	7	0	0	2

B: Pattern of functionally connected voxels in auditory cortex

Patient and Seed Voxel Cluster	Seed Voxel in L Hemisphere: No. of Voxels in the LH	Seed Voxel in L Hemisphere: No. of Voxels in the RH	Seed Voxel in R Hemisphere: No. of Voxels in the LH	Seed Voxel in R Hemisphere: No. of Voxels in the RH
A, 1	6	0	0	3
B				
1	6	0	0	9
2	7	0	0	5
3	5	0	0	7
4	9	0	0	10
5	NA	NA	0	9
C, 1	5	0	0	3

Note.—The seed voxels were correlated with every other voxel in the data set, and voxels exceeding a threshold of 0.4 ($P < .01$) were classified as functionally connected. LH indicates the left hemisphere; RH, right hemisphere; NA, not applicable (three patients had different number of clusters in each hemisphere).

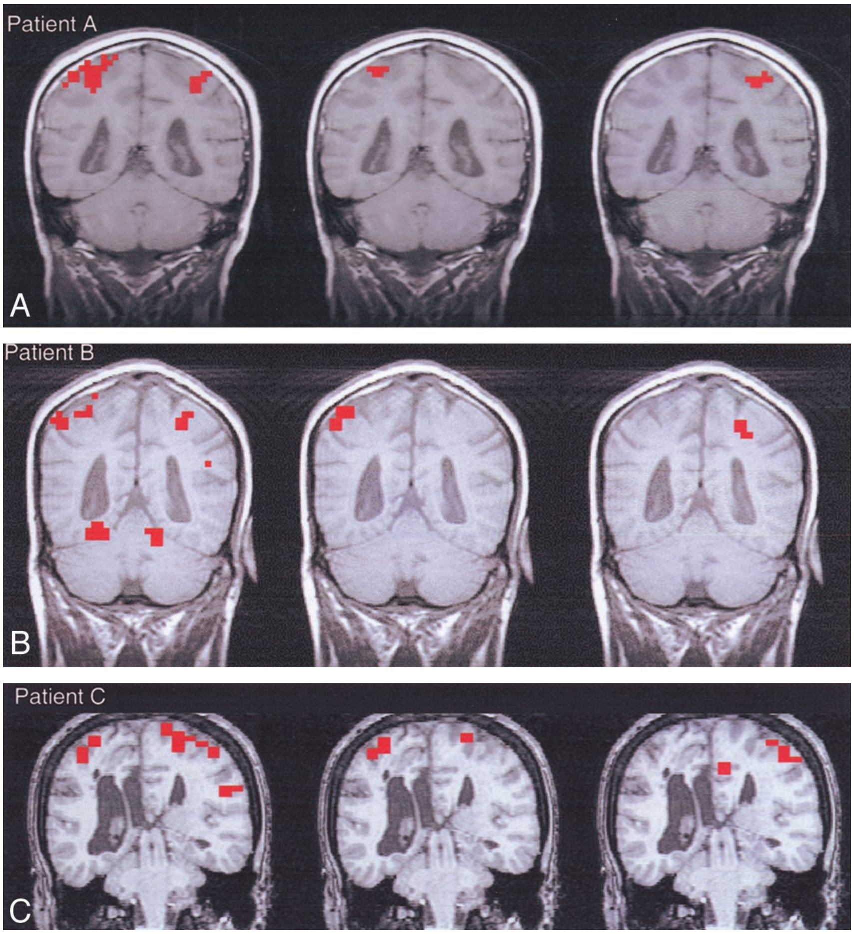

FIG 1. Functional connectivity and activation in the sensorimotor cortex of the three patients with agenesis of the corpus callosum. *Left*, Image displays the activation data from sensorimotor cortex identified by bilateral finger tapping. *Middle*, Image displays the functional connectivity data as the voxels functionally connected with a seed voxel cluster were chosen in the right sensorimotor cortex. *Right*, Image displays the functional connectivity data as voxels functionally connected to a seed voxel were selected in the left sensorimotor cortex. Note that with one exception (*middle* image in *C*), all functionally connected voxels are in the hemisphere ipsilateral to that of the seed voxel.

A, Patient A.
B, Patient B.
C, Patient C.

car function (idealized expected response to the task), which was smoothed by convolution with a Poisson function with 6-second mean. The amplitude and the uncertainty of the fit to the box car reference function were calculated. A t score was calculated to estimate the significance of the response to the task. Activation maps were created by setting a threshold t score value. The t maps were merged with anatomic images and viewed by using AFNI software (7).

For the functional connectivity analysis, seed voxels were selected from the resting data set that demonstrated activation during the performance of a task. The seed voxels were correlated with every other voxel in the data set, and voxels exceeding a threshold of 0.4 ($P < .01$) were classified as functionally connected. The numbers of functionally connected voxels in the ipsilateral and contralateral eloquent regions were tabulated.

Results

For all patients, standard functional MR task activation maps of good technical quality were obtained. Activation was identified in the superior temporal lobe for text listening and in the sensorimotor cortices, supplementary motor areas, and dentate nucleus for finger tapping (Table, part A).

The maps resulting from the connectivity analysis showed clusters of voxels in locations similar to those of the activated task data. For each seed voxel selected in the sensorimotor cortex of each patient, clusters of voxels were identified in locations similar to those demonstrated during task activation (Fig 1). In patient 1, the four seed voxel clusters in the left sensorimotor cortex had functional connectivity with five, six, eight, or 10 voxels in the ipsilateral sensorimotor cortex and with none in the contralateral sensorimotor cortex. This result implies that the functional connectivity is ipsilateral, not contralateral, for primary sensorimotor cortex, likely because of the lack of the corpus callosum. The single seed voxel cluster selected in the right sensorimotor cortex had six functionally connected voxels in the ipsilateral cortex and none in the contralateral sensorimotor cortex. For patient 2, the seed voxel clusters in the left sensorimotor cortex were functionally connected with six, seven, eight, 10, or 19 voxels in the ipsilateral sensorimotor cortex and zero to seven voxels in the contralateral hemisphere. Seed voxels in the right hemisphere were functionally connected with six, 12, 14, or 17 voxels in the ipsilateral sensorimotor cortex and zero to seven in the contralateral hemisphere. For patient 3, each of the two voxels clusters selected in the left sensorimotor cortex had seven or eight ipsilateral and no contralateral functionally connected voxels. In this patient, one seed voxel selected in the right sensorimotor cortex had five ipsilateral and two contralateral functionally connected voxels; the other seed voxel selected in the right sensorimotor cortex had no functionally connected voxels in the contralateral hemisphere.

The pattern of functionally connected voxels in the

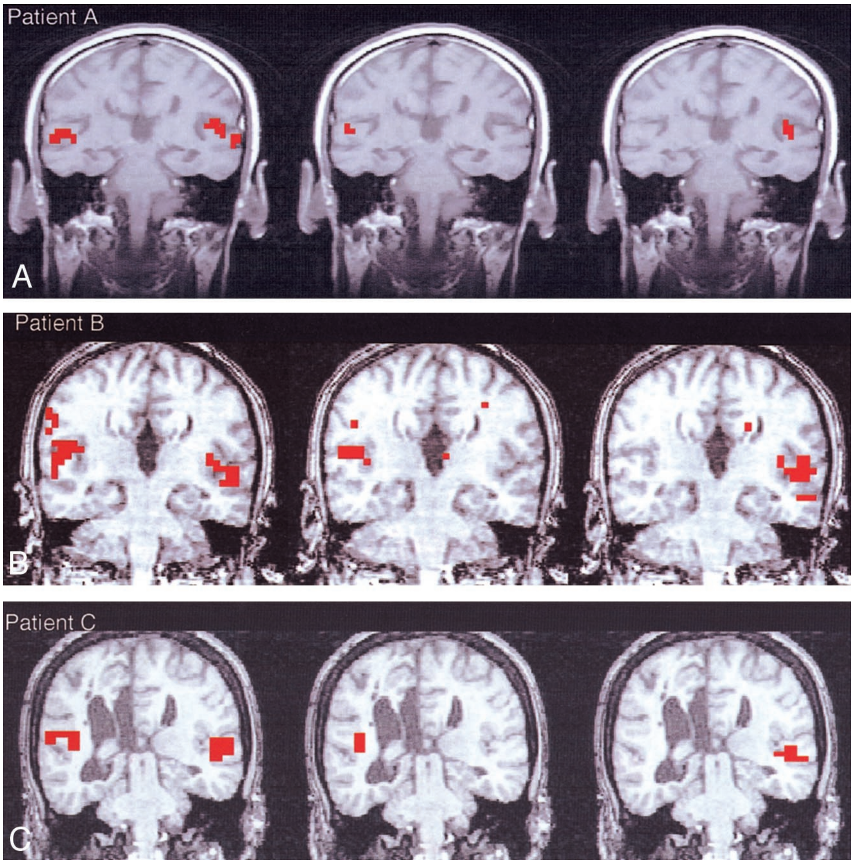

FIG 2. Functional connectivity in the auditory cortex of the three patients with agenesis of the corpus callosum. *Left*, Image displays the activation data from the auditory cortex during a text-listening task. *Middle*, Image displays the functional connectivity data as the voxels functionally connected to a seed voxel cluster were chosen in the right auditory cortex. *Right*, Image displays the functional connectivity data as voxels functionally connected to a seed voxel were selected in the left auditory cortex.

A, Patient A.

B, Patient B.

C, Patient C

auditory cortex is summarized (Table, part B). In patient 1, for a voxel cluster in the left sensorimotor cortex and one in the right auditory cortex, six and nine voxels in the ipsilateral cortex and none in the contralateral cortex demonstrated functional connectivity. In patient 2, voxels clusters selected in the left and right sensorimotor cortex demonstrated five to 10 ipsilateral functionally connected voxels and no contralateral functionally connected voxels. In patient 3, the voxel clusters in the left and right auditory cortex demonstrated ipsilateral functional connectivity but not contralateral connectively (Fig 2).

In each of the three subjects, the number functionally connected voxels in eloquent cortex ipsilateral to the seed voxel greatly exceeded the number of functionally connected voxels in the contralateral cortex. The null hypothesis that no difference exists between the number of functionally connected voxels in the ipsilateral and contralateral hemispheres was tested with the Wilcoxon signed rank test. The probability that the null hypothesis is correct was $P = .01$ for sensorimotor and auditory cortex.

For comparison purposes, a functional connectivity analysis was undertaken in a healthy volunteers with an intact corpus callosum. The results are shown in Figure 3. In contrast to the patient data, one can clearly see connectivity both ipsilateral and contralateral to the seed voxel. This finding implies connectivity between the hemispheres.

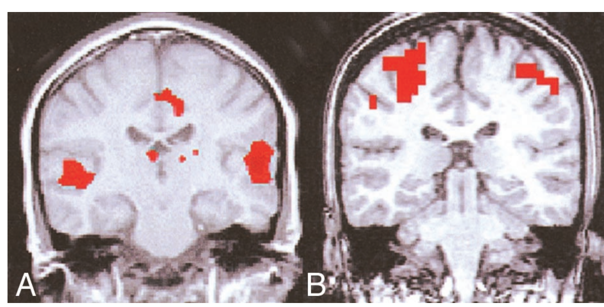

FIG 3. Functional connectivity maps from healthy control subjects with an intact corpus callosum. Notice the bilateral connectivity in both maps in contrast to the agenesis data shown in Figures 1 and 2.

A, Seed voxel chosen from the right auditory cortex.

B, Seed voxel chosen from the right sensorimotor cortex.

Discussion

The results of this study show that interhemispheric connectivity is reduced in patients with agenesis of the corpus callosum. For every voxel cluster selected, the number of functionally connected voxels in the ipsilateral hemisphere exceeded that in the contralateral hemisphere. This result contrasts with high interhemispheric connectivity reported in healthy subjects and in patients with an intact corpus callosum (1, 2). The methods were used in this study were essentially identical to those used in studies that demonstrated functional connectivity distributed between hemispheres in healthy subjects and in patients with an intact corpus callosum (2).

Results in a functional connectivity study greatly depend on the choice of the seed voxel and on the threshold chosen. As voxel position is varied, fewer or more functionally connected voxels are identified. We used voxel clusters to reduce the effect of sampling errors. We attempted to sample as much of the region of activation as possible by selecting a series of voxel clusters. We sampled only voxels within regions of eloquent brain that demonstrated activation, to minimize the effect of a selection bias. As thresholds are varied, the number of functionally connected voxels in both the ipsilateral and the contralateral cortex varies. Functional connectivity in the contralateral hemisphere was lacking over a wide range of thresholds in the patients with agenesis of the corpus callosum just as it is present over a wide range of thresholds in healthy subjects.

The corpus callosum contains interhemispheric connections for the sensorimotor and auditory cortices (8). Agenesis of the corpus callosum decreases the interhemispheric connections for the sensorimotor and auditory cortices. In these patients, connections between hemispheres through the anterior commissure and other interhemispheric commissures are presumably present. Functional connectivity to a seed voxel in a contralateral hemisphere can be demonstrated in patients with agenesis of the corpus callosum at thresholds much lower than those in healthy subjects. However, at this threshold level, differences in the data are no longer statistically significant. The degree to which connectivity is diminished in agenesis of the corpus callosum can be determined when more suitable methods for measuring the connectivity are developed. Under development are additional techniques to measure functional connectivity without the need to select seed voxels and to increase the accuracy of the functional connectivity measurements.

Patients with agenesis of the corpus callosum demonstrate clinical deficiencies due to diminished connectivity. Psychological testing demonstrates that agenesis of the corpus callosum is associated with altered function on tasks requiring sensory integration of visual and tactile information across the body midline (9–11). Patients with agenesis have evidence of disconnection in some language tasks but not in others (12). Language delays are reported in patients with defects in the corpus callosum (13). Some types of integration are achieved through the anterior commissure (14, 15) or other pathways (16). The corpus callosum may also mediate activation in the ipsilateral hemisphere in patient performing a unilateral motor task (17).

This study provides further documentation that the synchronous fluctuations in blood flow in eloquent regions of the hemispheres are a manifestation of functional connectivity. Although functionally connected voxels are present in both the ipsilateral and contralateral hemispheres in healthy subjects, they are found only in the ipsilateral hemispheres in patients with agenesis of the corpus callosum when the same techniques are used. Functional connectivity is a manifestation of connections between functionally related brain regions.

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