Clinical Investigative Study

Further Evidence for the Topography and Connectivity of the Corpus Callosum: An fMRI Study of Patients with Partial Callosal Resection

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ABSTRACT

BACKGROUND AND PURPOSE

This functional MRI study was designed to describe activated fiber topography and trajectories in the corpus callosum (CC) of six patients carrying different degree of partial callosal resection.

METHODS

Patients receiving gustatory, tactile, and visual stimulation according to a block-design protocol were scanned in a 1.5 Tesla magnet. Diffusion tensor imaging (DTI) data were also acquired to visualize spared interhemispheric fibers.

RESULTS

Taste stimuli evoked bilateral activation of the primary gustatory area in all patients and foci in the anterior CC, when spared. Tactile stimuli to the hand evoked bilateral foci in the primary somatosensory area in patients with an intact posterior callosal body and only contralateral in the other patients. Callosal foci occurred in the CC body, if spared. In patients with an intact splenium central visual stimulation induced bilateral activation of the primary visual area as well as foci in the splenium itself.

CONCLUSION

Present data show that interhemispheric fibers linking sensory areas crossed through the CC at the sites where the different sensory stimuli evoked activation foci, and that topography of callosal foci evoked by sensory stimulation in spared CC portions is consistent with that previously observed in subjects with intact CC.

Keywords: Callosal commissure, interhemispheric transfer, split-brain patients, functional brain imaging, DTI.

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Ethical Statement: The authors declare that the experiments were undertaken with the understanding and written consent of each subject, and that the study conforms with The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the *British Medical Journal* (18 July, 1964). The study was approved by the Ethics Review Board of the Medical Faculty of Università Politecnica delle Marche, Ancona.

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Background and Purpose

The corpus callosum (CC) connects the cerebral hemispheres and provides for integration and transfer of information. Electrophysiological and neuroanatomical data in nonhuman primates[1,2] and human investigations[3] suggested that the CC is endowed with a topographical organization.

This hypothesis has been confirmed by data obtained in subjects with CC lesions or resection.[4–6] Behavioral studies have shown that somatosensory transfer is preserved only in patients with frontal commissurotomy.[7,8] Other studies have shown that lesions of anterior CC sparing the splenium impair interemispheric transfer of somatosensory and auditory information.[9]

Lesions extending to the anterior splenium left intact only visual transfer. Resection of the sole splenium abolishes interhemispheric transfer of visual information but not in other sensory modality.[10] The hypothesis of callosal channels is reinforced by Funnel et al[11] by showing that the transfer of some visual information (read words) but not of others (color and shape) occurred in a patient with few fibers spared in posterior and anterior CC. A recent study of nonepileptic patients with transection of different portions of the anterior CC[12] showed that the middle part of the genu is involved in motor coordination and the anterior portion of the body in the transfer of somaesthetic information. Other investigations confirmed that the splenium is crucial for the interhemispheric transfer of visual[13] as well as for auditory information.[14,15] Functional magnetic resonance imaging (fMRI) investigations on patients with resection the posterior callosal body[6,16,17] confirmed that this portion is the tactual channel.

In recent years, fMRI studies have described in the CC a blood oxygen level dependent (BOLD) activation, i.e. an increase of local blood flow induced by increased neural activity, during behavioral tasks involving interhemispheric transfer.[18–22] This observation seems to confirm that the anterior CC is involved in exchange between prefrontal and premotor regions, the posterior CC in transfer between parietal, occipital, and temporal cortices.[23–26] Moreover, this observation also suggests that white matter fibers activity too, namely of the callosal ones, could evoke an increase of local blood flow, which is likely due to energy-dependent processes as axon conduction. The greater metabolic demand from such increased activity likely induces vessel dilation that could in turn be mediated by an increased vasodilatory neurotransmitter release in the extracellular environment (see Section "Discussion" for a more detailed description).

A recent fMRI study in normal subjects evidenced the presence of callosal activation foci and their topographical organization: anterior CC was activated by taste stimuli, central CC by motor tasks, central, and posterior CC by tactile and splenium by visual stimuli (Fig S1[27]).

To further document the possibility to obtain a functional CC map by analyzing the callosal BOLD response, we report an fMRI study where the peripheral sensory stimulation protocols applied in healthy subjects were administered to partial callosotomy patients. The results were analyzed for evidence of a specific BOLD effect in the extant callosal portions. Diffusion tensor imaging (DTI) data were acquired to visualize spared callosal fibers, and to establish whether CC activation was colocalized with tracts seeded from activated clusters in cortical areas involved by specific sensory stimuli.

Preliminary results have been presented in abstract form.[28–30] Part of present data were included in a previous review.[31]

Methods

Subjects

Data were collected from 6 callosotomy patients (age range 22–51 years, 2 women) during studies of gustatory, tactile, and visual cortical representation. The callosotomy, performed to treat drug-resistant epilepsy, involved the anterior CC, although in different degree, in 4 subjects (P2, 3, 4, and 5), the posterior CC in one (P1) and the central CC in the last patient (P6) (Fig S2). All patients gave their informed consent to participate in the study, which was approved by the Ethics Review Board of the Medical Faculty of Università Politecnica delle Marche (Ancona). Hence, this study fully conforms with the code of ethics of the World Medical Association [Declaration of Helsinki; see Br Med J (July 1964), [818]. Handedness was evaluated by the Oldfield inventory.[32] Tactile stimulation was applied to all 6 patients, visual stimulation to 5 (P1, P2, P3, P5, and P6), and gustatory stimulation to 4 patients (P1, P3, P4, and P6) (Table S1). Stimuli were applied according to a block-design protocol where periods of rest were alternated with periods of stimulation. Taste and touch stimuli were applied to the left or right side in different sessions; visual stimuli were presented to the left or right visual field in the same session, or to the central visual field in a separate session (Section "Methods" of Additional Supporting Information).

Imaging Protocols

For all investigations subjects were placed in a 1.5-tesla (T) scanner (Signa Excite NV/i CV/i, General Electric Medical System, Milwaukee, WI, USA) equipped with 50 mT/m gradients, with their head restrained within a circularly polarized head coil. They were instructed to keep their eyes closed, find a comfortable position and relax, avoiding even minimal movement.

Functional Imaging

A 4-step experimental procedure was applied for all examinations. First, an anatomical three-plane localizer was acquired (2D SPGR, TR 120 ms, TE 15 ms, Flip Angle 70°, FOV 23 × 23 cm, slice thickness 5 mm, Matrix 256 × 256, 1 Nex, scan time 31 s). The second step entailed acquisition of a 3D dataset (IR Prep Fast SPGR; TR 15.2 ms, TE 6.9 ms, TI 500 ms, Flip Angle 15°, FOV 29 × 29 cm, slice thickness 1 mm, Matrix 288 × 288, 1 Nex, and scan time 8:20 min). The third step involved the acquisition of 1,000 (2,000 in more recent studies) functional images (or volumes) from 10 (20 in more recent studies) axial (or oblique) planes selected to cover the brain region to be studied (100 images from each plane; (Fig 1) with a single-shot T2*-weighted gradient-echo EPI sequence (TR 3000 ms, TE 60 ms, Flip Angle 90°, FOV 28 × 21 cm, Matrix 96 × 64, 1 Nex, scan time 5:12 min). In the fourth step 10 (20 in more recent studies) contiguous 5-mm-thick high-resolution axial (or oblique) anatomical images were acquired from the same 10 (20) planes selected in the third step (1 image per plane; 2D SPGR, TR 100 ms, TE 12 ms, Flip Angle 70°, FOV 28 × 21 cm, thickness 5 mm, Matrix 256 × 256, 1 Nex, scan time 3:17 min for 10 images) so that functional activation images could be superimposed onto the anatomical landmarks, to visualize blood vessels that are possible sources of BOLD signal. Other details on images acquisition are described in Section "Methods" of Additional Supporting Information.

Diffusion Tensor Imaging

The connections between activated cortical areas were studied by means of DTI, to establish whether CC regions crossed by interhemispheric fibers reconstructed using diffusion

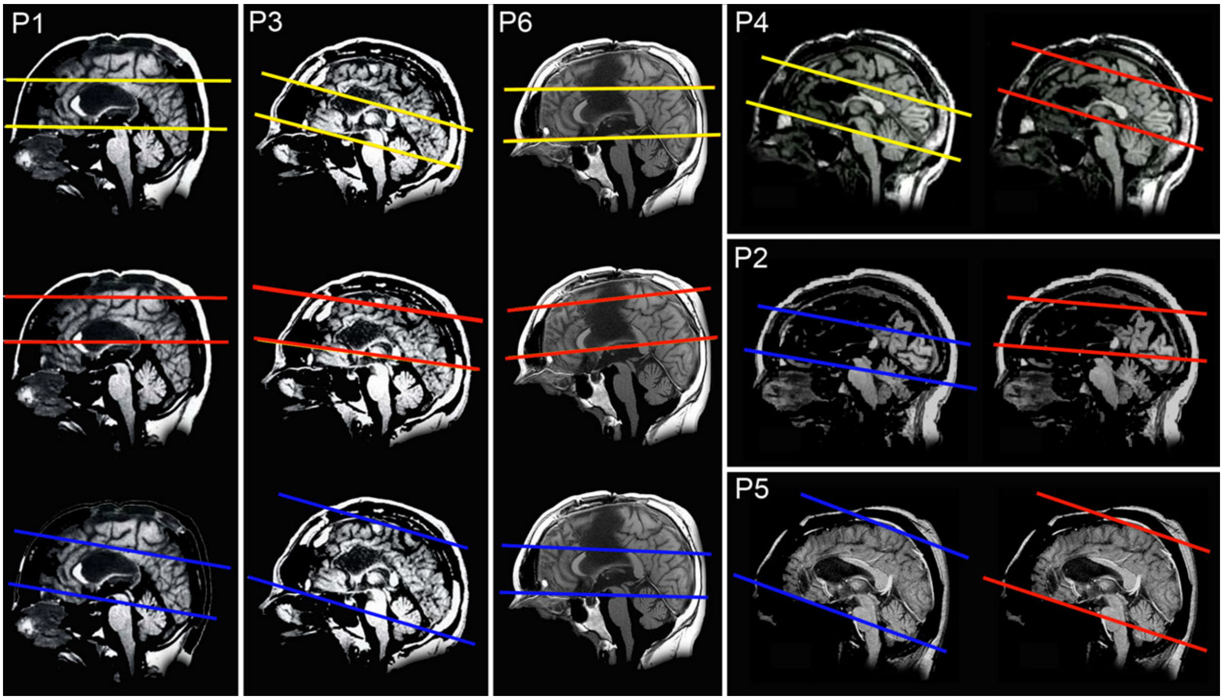

Fig 1. Brain regions from which functional and anatomical images were acquired in patients during different stimulation sessions. P1, P3, and P6 received all three kind of stimulation: brain volume scanned during taste stimulation is showed between yellow lines (top row brain figurines); that scanned during hand touch stimulation is showed between red lines (middle row brain figurines), and that scanned during visual stimulation between blue lines (bottom row brain figurines). P4 received taste and touch stimulation: brain volume scanned during taste stimulation is indicated between yellow lines (top row brain figurines), and that scanned during hand touch stimulation between red lines (middle row brain figurines). For P2, receiving touch and visual stimulation, brain volume scanned during hand touch stimulation is included between red lines, and that scanned during visual stimulation is between blue lines. P5 received visual and touch stimulation; brain volume scanned was the same in both session and is shown between blue and red lines, respectively. In this patient and in P3 visual stimulation 20 oblique axial planes were scanned, in all other cases 10 planes. For all images posterior pole is on the right.

tensor tractography (DTT) were linked to areas where a BOLD effect had been observed. For this study a series of oblique axial images was obtained using a single shot spin-echo echo-planar sequence with a diffusion-sensitizing gradient. Diffusion was measured along 25 noncollinear directions. The *b*-value was 1000 s/mm^2. Acquisition parameters were: TR 6500 ms, TE 76.2 ms, Matrix 128 × 128, FOV 26 × 26 cm, slice thickness 5.0 mm, interslice gap 1.0 mm, Nex 2, scan time 5:51 min (Section "Methods" of Additional Supporting Information).

Stimulation Protocols

Taste stimulation was applied to 4 patients, *tactile stimulation* to all 6 patients and *visual stimulation* to 5 patients. A detailed description of different stimuli applied and the administration modality is provided in Supplementary Material (Section "Methods"; Table S1).

Data Analysis

After each experimental session images were transferred to a Unix workstation (General Electric Advantage Windows 4.2) and then to a PC. Data were analyzed with the BrainVoyager QX (BV QX) software (Brain Innovation, Maastricht, The Netherlands). 3D anatomical data were preprocessed with intensity inhomogeneity correction and spatial transformation, then transformed to Talairach standard space. Coregistration of functional and anatomical data resulted in a normalized 4D volume time course data, which allowed transformation of functional time series into Talairach space and identification of the position of activated areas using the Talairach coordinate system.

For DTI data analysis, images were transferred post-processed with Functool 3.1.22 (General Electric Medical Systems). The FiberTrak option allows Functool to create 3D tractography maps. The detailed description of functional and DTI data analysis, statistical analysis, and ROIs definition is provided in Section "Methods" of Additional Supporting Information.

Results

Peripheral sensory stimulation evoked cortical activation in the corresponding primary sensory area (Table S2) and elicited foci in the extant CC. The cortical areas activated and the sites of the callosal foci depended on stimulus characteristics, as described below.

Functional Imaging

Gustatory stimulation (4 patients). A salty stimulus applied to each side of the tongue in separate scanning sessions (Table S1) induced bilateral activation of the primary gustatory area (GI) in the fronto-parietal operculum in all 4 patients (Table S2; Fig 2; see[33]). In the 2 subjects whose anterior CC was spared (P1 and P6) the same stimulus also evoked a callosal focus in

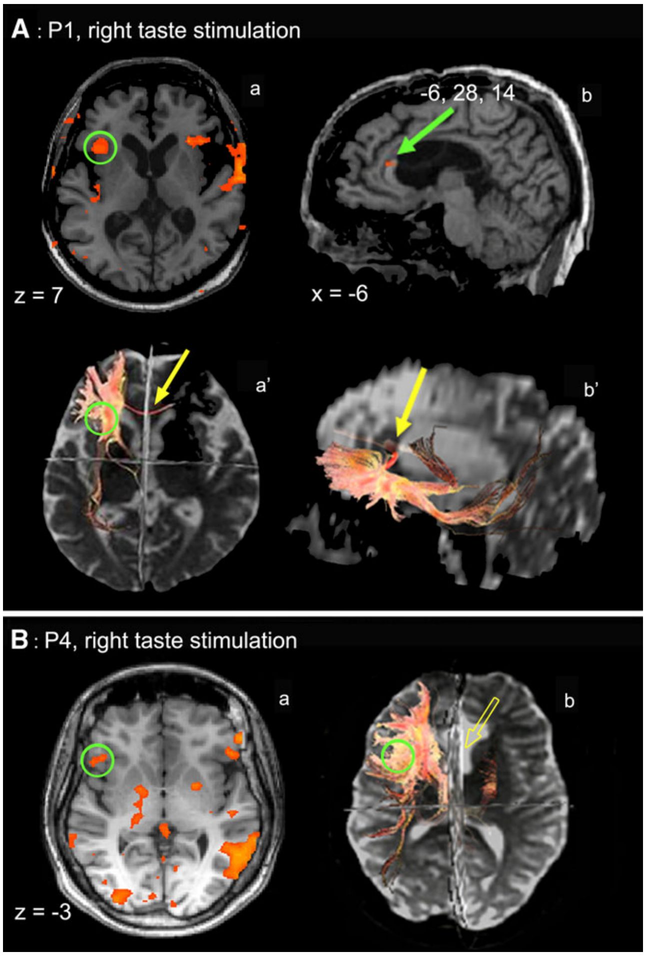

Fig 2. Activation evoked by taste stimulation in patients 1 (A) and 4 (B). Bilateral cortical activation (fronto-parietal operculum) is seen in both patients. Patient 1 also displayed a callosal focus (Ab, green arrow). Fibers arising from the activated cortex cross the CC through the anterior callosal portion in patient 1 (Aa' and b', yellow arrows), but in patient 4 they do not reach the contralateral hemisphere (Bb, yellow empty arrow). For axial images, left hemisphere is on the right; for sagittal images, posterior pole is on the right.

the anterior CC (Fig 2Ab, 6A). The mean y coordinate of the callosal foci was 22.5 (Table S3; $P < 0.05$).

In these 2 patients interhemispheric fibres crossing through the spared anterior CC are visible (Fig 2Aa' and b'), as detailed below. In the other 2 patients (P3 and P4) and in P6 an activation focus was also noted in the posterior CC (mean y coordinate: −35.33; Table S3; Fig 6A). Coordinates of both anterior and posterior foci evoked by taste stimulation were similar to that observed in healthy subjects, although for taste stimuli different from salty.[27]

Tactile stimulation (6 patients). Unilateral tactile stimuli applied to the left or right hand (Table S1) activated the primary (SI) and the secondary (SII[16,17,34]) somatosensory area in the contralateral parietal cortex in all 6 patients. In addition, the 3 patients whose posterior callosal body (PCB) was spared (P4, P5, and P6) exhibited different activation patterns that included bilateral activation of the posterior parietal (PP) cortex and SII

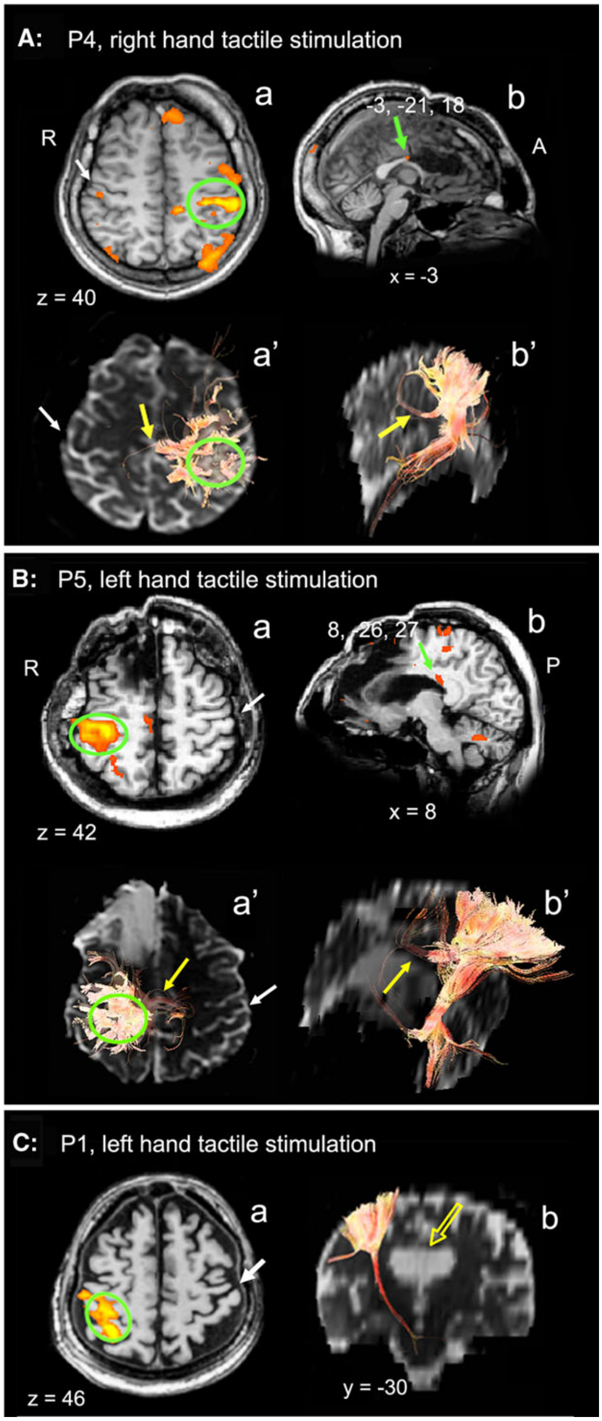

Fig 3. Activation evoked by tactile stimulation of the hand in patients 4 (A, right hand), 5 (B, left hand), and 1 (C, left hand). Activation in the anterior parietal cortex is seen in all three patients but is bilateral in patient 4. Callosal activation is observed only in P4 and P5. Fibers arising from the activated cortex cross the CC through its central portion (Aa'-b' and Ba'-b', yellow arrows). In P1, fibers arising from the activated cortex (Ca, green circle) do not reach the opposite hemisphere, as shown in the coronal image, due to the interruption of callosal fibers (Cb, empty yellow arrow). For axial and coronal images, left hemisphere is on the right; for sagittal images, posterior pole is on the left in A, on the right in B. A = anterior; L = left; P = posterior; R = right.

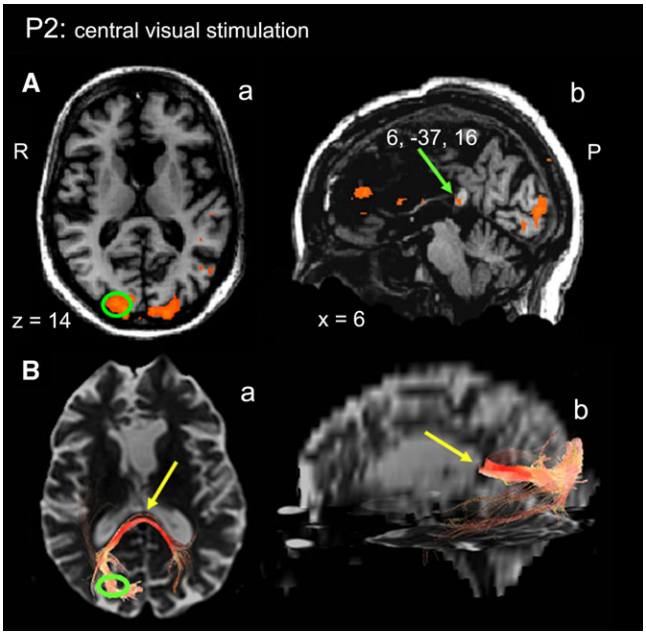

Fig 4. Activation evoked by central visual stimulation in patient 2. Cortical activation is seen in the occipital cortex of both hemispheres and in the callosal splenium (Ab, green arrow). Fibers arising from the activated cortex cross the CC through the extant part of the splenium (Ba and b, yellow arrows). For axial images, left hemisphere is on the right; for sagittal images, posterior pole is on the right. P = posterior; R = right.

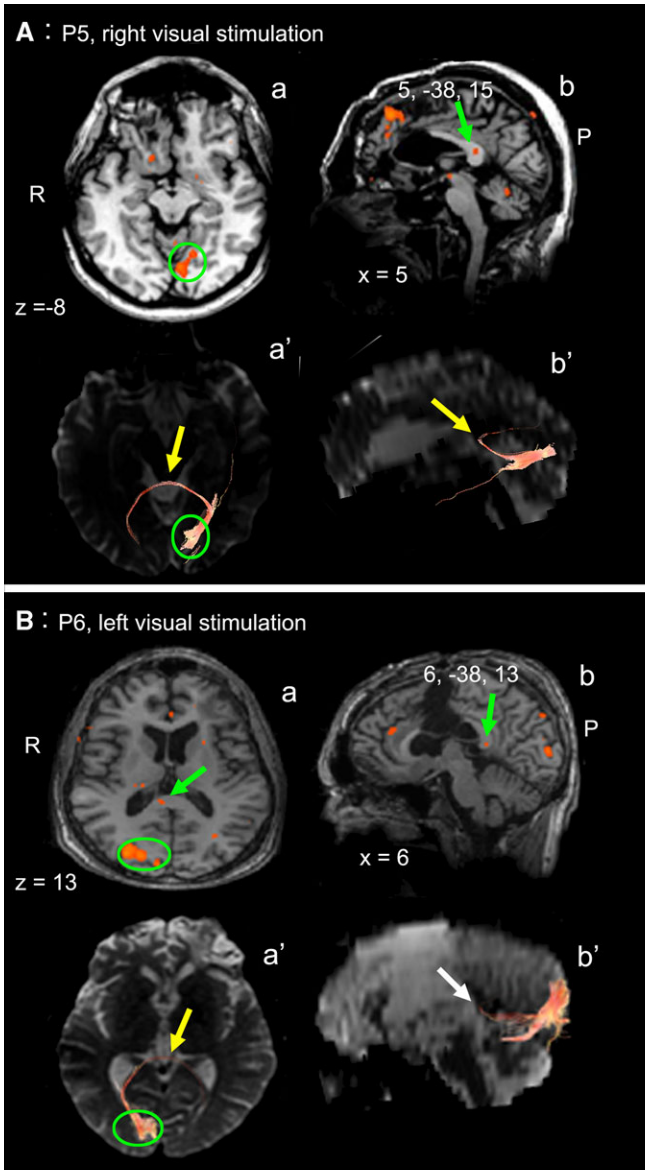

Fig 5. Activation evoked by peripheral visual stimulation in patient 5 (A, stimulus in RVF) and 6 (B, stimulus in LVF). Cortical activation is seen in the occipital cortex of the contralateral hemisphere (left hemisphere in A and right hemisphere in B) and in the callosal splenium (Ab and Bb, green arrows). Fibers arising from the activated cortex cross the CC through the spared portion of the splenium (Aa'- b' and Ba'- b', yellow arrows). Note that in VI the fiber bundle arising from the representation of the peripheral retina and crossing the splenium is much thinner than the bundle arising from the foveal representation, pictured in Figure 4. For axial images, left hemisphere is on the right; for sagittal images, posterior pole is on the right. A = anterior; L = left; P = posterior; R = right.

(P4; Fig 3Aa); bilateral PP activation only (P5); and bilateral SII activation only (P6). In the other patients (P1, with posterior callosotomy, P2 with a small part of the splenium spared and P3 with the only splenium spared), cortical activation was only contralateral. Tactile stimuli also evoked callosal foci, more frequently in the PCB, in patients in whom this central CC region was spared (P4, P5, and P6; Fig 3Ab and Bb). The y coordinate ranged from −19 to −26 (see mean values in Table S3), very similar to that observed in healthy subjects.[27] In these patients interhemispheric fibres crossing through the CC (Fig 3Aa'-b' and Ba'-b') were also detected at sites harboring CC activation foci. Other than PCB focus, P5 exhibited an additional focus in the anterior callosal midbody (ACB; Fig 6B) and another in the splenium (Fig 6B; Table S3), while P4 and P6 showed an additional focus in the splenium (Fig 6B; Table S3). In patients in whom the PCB was lacking no activation was observed within the CC (Fig 3C).

Visual stimulation (5 patients). Unilateral visual stimuli presented to the peripheral LVF or RVF, or to the CVF (Table S1) induced activation foci in VI in all 5 patients (Table S2; Fig 4A) for CVF stimulation and (Fig 5A and B for peripheral VF stimulation). VI activation was usually bilateral after CVF stimulation, and contralateral after peripheral VF stimulation. In patients whose splenium was spared an activation focus was observed in this region (Figs 4Ab and 5). The values of the *y* coordinate ranged from −32 to −38 (mean values in Table S3; Fig 6C), consistent with control values (mean −35[27]). The interhemispheric fibers linking the activated visual areas crossed through the extant splenium (Figs 4B and 5) at sites harboring the BOLD foci.

Tractography

Processing of DTI and DTT data showed that fractional anisotropy (FA) values in the CC regions crossed by fibers linking activated areas were similar to those reported in

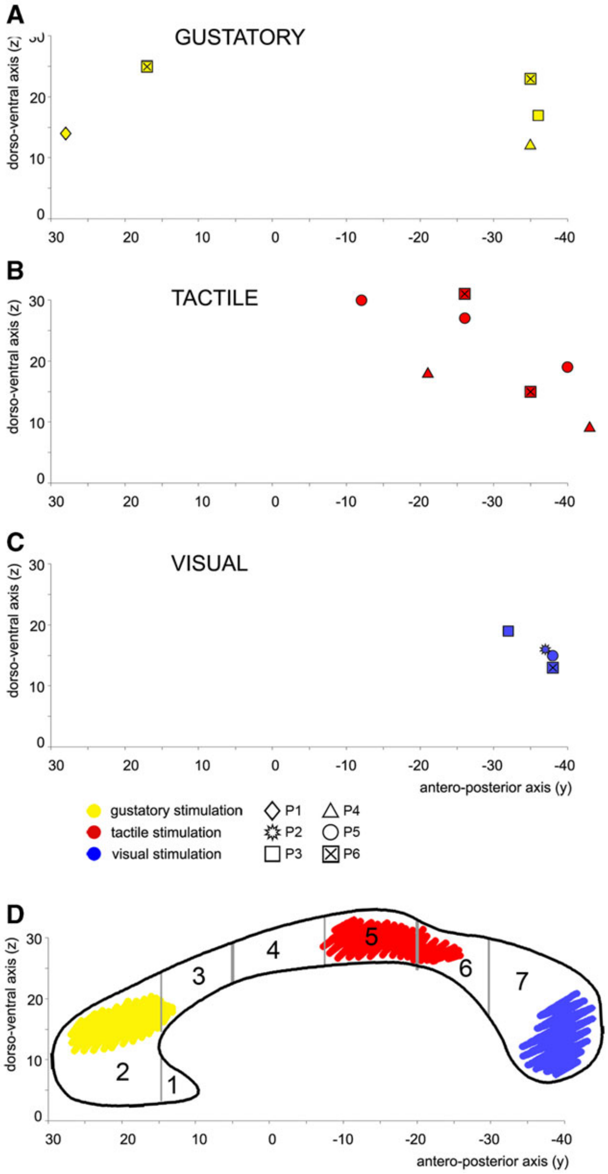

Fig 6. Summary schematic diagram showing the distribution of the callosal activation foci evoked by different stimulus types in callosotomized patients. (A–C) Each dot represents the *y* and *z* Talairach coordinates (reported on the respective Cartesian axes) of the foci evoked by different stimuli. (A) Foci evoked by gustatory (salty) stimulus; (B) foci evoked by hand tactile stimulus; (C) foci evoked by visual stimuli. See the text for a detailed description. (D) shows the crossing sites of interhemispheric fibers connecting the sensory cortical areas activated by the relevant peripheral stimuli. The outline of the CC has been positioned according the Talairach coordinates; vertical gray lines mark the main CC subdivision according to Witelson S. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. *Brain* 1989; 112: 799-835. The colored tracts mark the CC crossing sites of fibers from frontal opercular cortical areas (yellow), anterior and posterior parietal cortices (red), occipital cortices (blue).

previous studies on healthy subjects[35–37] and that they were not significantly different among CC regions. In particular, FA was 0.68 in the spared genu (healthy subjects 0.72, $P > 0.05$), 0.61 in the PCB (healthy subjects 0.69, $P > 0.05$) and 0.73 in the splenium (healthy subjects 0.68, $P > 0.05$[37,38]).

Callosal fibers arising from individual cortical ROIs. Examination of the fibers arising from a cortical ROI selected in area GI (Fig 2Aa, green circle) showed that they crossed through the anterior part of the CC (genu; Fig 2Aa', axial view, and 2Ab', sagittal view; Fig 6D), i.e. the region activated by taste stimuli, whereas no fibers from area GI were seen to cross through the CC at the level of the splenium. Fibers from an ROI selected in the medio-lateral parietal cortex activated by tactile stimulation of the hand (hand zone of SI; Fig 3Aa and Ba, green circles) crossed through the CC slightly more posterior (Fig 3Aa'-b' and 3Ba'-b'; Fig 6D), i.e. the region activated by hand touch stimuli, whereas no fibers from area SI were seen to cross through the CC at the level of the splenium. Analysis of an ROI selected in the activated region of VI (Figs 4Ba-b and 5Aa'-b' and Ba'-b') showed fibers crossing through the splenium (Figs 4B and 5A–B; Fig 6D), at a site activated by visual stimuli.

Callosal ROIs. When ROIs were selected in parts of the genu, anterior body, PCB and splenium harboring activation foci, the callosal fibers were seen to interconnect respectively the fronto-parietal opercula and prerolandic, parietal, occipital, and temporal regions, which bore foci activated by taste stimulation of the tongue, hand motor tasks, tactile stimulation of the hand and trunk and visual stimulation, respectively (Fig S3[30]).

Even though activation foci were seen in the splenium of some patients after taste or touch stimulation, no interhemispheric fibers from gustatory or somatosensory cortical areas were seen to cross through the CC at this level; similarly, no callosal fibers were seen to run from the foci in the splenium to cortical regions other than occipital or temporal areas.

Discussion

This fMRI study was designed to describe activated fibre topography and course in the CC of six partial callosotomy subjects with different sites and extents of callosal resection. Our findings add to the existing evidence by documenting that: (i) fMRI is capable of detecting the BOLD effect evoked by peripheral sensory stimuli in the extant CC; (ii) CC activation foci occupy consistent sites in the spared CC that are related to the type of sensory stimulus applied; and (iii) the resulting topographical CC map is in line with human postmortem data,[3] with studies of patients with CC injury or surgical resection[9,12,16,17,39–42] (see[4] and[5], for a review), and with electrophysiological recording and neuroanatomical animal studies.[1,2]

Cortical Activation

The pattern of cortical areas activated by each sensory peripheral stimulation is consistent with previous knowledge, i.e. fronto-parietal operculum (GI) after taste stimulation, anterior (SI), and posterior (PPC) parietal cortex and upper bank of the sylvian sulcus (SII) after tactile stimulation and occipital cortex in the calcarine sulcus (VI) after visual stimulation. The presence of bilateral activation of the respective sensory cortices was as expected according to the presence of callosal fibers except for gustatory areas: actually, bilateral activation of fronto-parietal opercula was observed also in absence of callosal fibers connecting them. Although a detailed explanation of this result is beyond the scope of the present paper, we can here suggest that bilateral activation of gustatory areas in absence of the CC could be supported by a subcortical mechanism.[33] The bilateral activation of SI and/or SII after tactile stimulation depends on the presence of callosal fibers in the PCB, as shown in previous papers by our group.[16,17,34]

Basis of callosal activation

A callosal BOLD effect has been previously documented after visual and motor stimulation[18–22] and, more recently, after sensory stimulation and simple motor tasks.[27] The increased blood flow could be due to energy-dependent processes as axon conduction at nodes of Ranvier level (see Section "Discussion" of Additional Supporting Information). As more extensively explained in the Section "Discussion" of Additional Supporting Information the BOLD effect is likely due to an increased neurotransmitter release in the extracellular environment and/or Ca^{++} concentrations in the astrocyte cytoplasm, which results in vessel dilation to meet the greater metabolic demand from such increased activity. For a more detailed discussion of this issue and the citation of related papers see Section "Discussion" of Additional Supporting Information.

Topography of Callosal Activation

Our present data from patients show that taste stimulation evoked activation foci in the anterior CC when this region is intact, at the site where interhemispheric fibers arising from the gustatory areas crossed through the commissure. Foci elicited by tactile stimulation of the hand were detected in the middle and posterior body, where interhemispheric fibers from somatosensory areas activated by touch stimuli were observed. In one patient a more anterior focus also was found, likely in the CC region where interhemispheric fibers from motor cortices cross through the commissure. These observations are generally consistent with previous findings obtained in healthy subjects,[27] in whom multiple foci of activations in CC are described for tactile hand stimulation, as done here: the anterior activation was often found in the motor callosal region, and it is likely due to activation of the primary motor cortex evoked by tactile stimulation[34]; the most posterior activation is described in healthy subjects at −30 (y coordinate), in a callosal region corresponding to the PCB. Foci elicited by visual stimuli were found in the splenium, as observed in healthy subjects,[27] in the CC region harboring interhemispheric fibers arising from occipital areas activated by visual stimulation. The coordinates of the CC sites bearing foci activated by central or peripheral VF stimulation were not significantly different.

In some patients callosal foci were evoked in the splenium by nonvisual stimuli, too. They were elicited (i) by taste stimuli in two subjects with anterior resection (P3 and P4) and in the one with central resection (P6; Fig 6A; Table S3) and (ii) by tactile stimulation of the hand in P6 and in two patients with anterior resection (P4 and P5; Fig 6B; Table S3). Similar data were found in our prior study of healthy subjects, although for gustatory stimulation a posterior activation was only found in these subjects after sweet and bitter stimulation, and tactile hand stimulation did not evidenced a focus in the splenium.[27] In a subsequent analysis of control subjects, however, activation foci were found in the splenium after tactile hand stimulation.[31] These differences might be due to interindividual differences, or to plasticity compensatory processes. They seem to be consistent with findings from previous behavioural investigations of callosotomy patients (see below).

The present study, showing CC activation evoked also by sensory stimuli not requiring interhemispheric transfer, suggests that all information reaching a cortical area is likely transferred to the opposite hemisphere and used to build a continuous representation of the external world.

Consistence with Tractography Data

The callosal topography sketched by the foci elicited in this study confirms findings obtained in healthy subjects.[27] DTI and DTT analysis of the data of each patient confirmed this organization, which agrees with the CC fibre organization described in previous studies[23,43–46] and with DTT data obtained in healthy subjects in our lab.[29] Fibers interconnecting prefrontal cortical areas crossed through the anterior part of the CC, if extant; those linking parietal cortical areas crossed through the spared PCB; and those between occipital areas crossed at the level of the splenium, where intact (see also[47–49]). In all tests, the fibers arising from cortical areas that were activated by each type of stimulus crossed the CC through a region that harboured the respective callosal focus/i. The coincidence of callosal BOLD activation and the crossing point(s) of DTT-reconstructed interhemispheric bundles strongly suggests that the CC foci evoked by sensory stimuli in partially callosotomy patients is likely due to the activation of fibers connecting activated areas. CC activation foci therefore closely corresponded to the CC crossing points of callosal fibers arising from cortical areas activated by specific peripheral sensory stimuli in our callosotomy patients.

Comparison with Other Human and Animal Studies

This is the first report of CC topography analyzing the contribution of fibers activated by different types of sensory stimuli in partial callosotomy patients. The resulting map agrees with the one found in a previous similar study of healthy subjects[27] and documents large interindividual differences that were not found in maps drawn from human postmortem or DTI investigations or monkey neuroanatomical studies. Often, multiple CC foci (usually two) were activated by each stimulus type; this was especially true of touch and taste stimuli. However, the multiple foci found in our subjects contrast with the single callosal sites identified by some DTT studies.[43–45] The discrepancy might be related to stimulus type, since DTI and monkey neuroanatomical studies examine the trajectories of fibres arising in circumscribed cortical areas, whereas the natural peripheral stimuli of our tests may have involved not only pure sensory and/or motor cortical areas, but a larger number of areas. Another explanation may be the well-documented interindividual anatomical and functional variability described in studies of behavioral lateralization tasks[50] strength of auditory area connectivity[51] and language lateralization.[52]

The two major findings of our previous study, i.e. the more posterior location of the fibers involved by sensory stimulation and the activation of multiple CC foci, of which at least one was in the splenium, were confirmed in this study. They are in line with neuropsychological studies of callosotomy patients and seem to explain some puzzling data, like the good performance in interhemispheric tactile transfer tasks of callosotomy patients in whom only the splenium is extant.[6,53,54] The involvement of the splenium in the transfer of tactile information is consistent with its activation by tactile stimulation of the hand, here described for the second time, and might be explained by the fact that natural peripheral stimulation may involve more numerous cortical areas than those classically believed to receive callosal fibers based on neuroanatomical tracing animal and DTI human studies. Further evidence of an unanticipated role of the splenium from neuropsychological studies of taste sensitivity in callosotomy patients[55,56] points to a role for the splenium in transferring taste information. The posterior callosal activation by unilateral taste stimulation found in this study lends support to this notion. An involvement of the splenium in the transfer of information other than visual sensory data could be related to the posterior displacement of parietal areas following the enlargement of association areas in the frontal lobes, and/or to interindividual variability, which sometimes allows partial recovery after excision of some callosal fibres. Finally, splenium activation could be ascribed to the prominent role of the visual representation of the external environment, typical of humans, where each sensory experience is associated with a visual component.

Conclusions

In conclusion, the data obtained in this study by applying simple sensory stimuli that did not involve a motor output nor necessarily interhemispheric transfer confirm that a BOLD effect may be detected in callosal WM and that activation foci evoked by different sensory stimuli are organized according to a topography that is known from other studies. In addition, although patients might not be representative for the healthy population, the presence of foci evoked in the splenium by nonvisual (tactile and gustatory) stimuli argues for a certain interindividual variability of the callosal functional topographical organization, also described by our group, and suggests that some reorganization process might have take place. Recent fMRI studies provided evidence, by mean of resting-state analysis, of a residual functional interhemispheric connectivity in callosotomized patients[57,58] that can be coordinated by subcortical brain structures. This residual activity, together with the above-mentioned interindividual variability of the callosal connectivity, could enable partial recovery often observed after resection of CC tracts.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

S–Methods

S–Discussion

Table S1. Characteristics of Patients and Types of Stimulation Administered

Table S2. Cortical Areas Activated after Application of Different Types of Peripheral Stimuli

Table S3. Talairach Coordinates of Callosal Activation Foci Evoked by Different Types of Peripheral Stimulation

Figure S1. (A–C) BOLD effect evoked in the CC of control subjects by gustatory, tactile, and visual stimulation, respectively (green arrows). Numbers are the Talairach coordinates of activation foci. (D–F) Sites where fibers connecting fronto-opercular, parietal, and occipital cortical areas, respectively, cross through the commissure (yellow arrows).

Figure S2. Midsagittal MR images from callosotomy patients showing the extent of callosal resection. Anterior pole on the left.

Figure S3. DTI images showing callosal fibers from ROIs selected in callosal regions where activation foci were evoked by different type of sensory stimuli. In each panel, the top brain figurine represents the structural view with the position of the ROI (white spot) and the bottom one the callosal fibers arising from it. A and B: ROIs in the genu in patients 1 (A) and 6 (B). D and E: ROIs placed in the posterior callosal body in patients 5 (C) and 4 (D). E, F, G, and H: ROIs placed in the splenium in patients 2 (E), 6 (F), 5 (G), and 3 (H). For axial images, left hemisphere is on the right; for sagittal images, posterior pole is on the right.