

Cortical lateralization of cheirosensory processing in callosal dysgenesis

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ABSTRACT

The paradoxical absence of a split-brain syndrome in most cases of callosal dysgenesis has originated three main hypotheses, namely, (i) bilateral cortical representation of language, (ii) bilateral thalamocortical projections of somatosensory pathways conveyed by the spinothalamic-medial lemniscus system, and (iii) a variable combination of (i) and (ii). We used functional neuroimaging to investigate the cortical representation and lateralization of somatosensory information from the palm of each hand in six cases of callosal dysgenesis (hypothesis [ii]). Cortical regions of interest were contralateral and ipsilateral S1 (areas 3a and 3b, 1 and 2 in the central sulcus and postcentral gyrus) and S2 (parts of areas 40 and 43 in the parietal operculum). The degree of cortical asymmetry was expressed by a laterality index (LI), which may assume values from -1 (fully left-lateralized) to $+1$ (fully right-lateralized). In callosal dysgenesis, LI values for the right and the left hands were, respectively, -1 and $+1$ for both S1 and S2, indicating absence of engagement of ipsilateral S1 and S2. In controls, LI values were -0.70 (S1) and -0.51 (S2) for right hand stimulation, and 0.82 (S1) and 0.36 (S2) for left hand stimulation, reflecting bilateral asymmetric activations, which were significantly higher in the hemisphere contralateral to the stimulated hand. Therefore, none of the main hypotheses so far entertained to account for the callosal dysgenesis-split-brain paradox have succeeded. We conclude that the preserved interhemispheric transfer of somatosensory tactile information in callosal dysgenesis must be mediated by a fourth alternative, such as aberrant interhemispheric bundles, reorganization of subcortical commissures, or both.

1. Introduction

1.1. The CD-split-brain paradox

The expression “callosal dysgenesis” (CD) encompasses a spectrum of malformations that ranges from hypoplasia through total or partial absence of the corpus callosum (CC) (Kendall, 1983). Patients with CD may be asymptomatic or present a range of symptoms such as epilepsy, mental and psychomotor retardation, and capricious associations of neuropsychological syndromes (Pisani et al., 2006; Moes et al., 2009; Siffredi et al., 2013; Bridgman et al., 2014; D'Antonio et al., 2016; Rehmel et al., 2016; Lábadi and Beke, 2017; Romaniello et al., 2017). A remarkable aspect of most cases of CD is the absence of a classical disconnection, or “split-brain”, syndrome (Ettlinger et al., 1972), which

is the rule in cases of surgical section (Sperry et al., 1969) or acquired (Zaidel et al., 2003) damage of the CC. This “CD-split-brain paradox” has provided a natural experiment on the mechanisms of brain reorganization in patients with congenital defects of the CC that has fruitfully been explored from diverse perspectives (Jakab et al., 2015; Paul et al., 2007; Tovar-Moll et al., 2007, 2014; Wahl et al., 2009). However, the plastic mechanisms that operate in CD to make up for the disconnection symptoms are still unknown.

1.2. Tactile anomia x tactile agnosia

The telltale sign of the split-brain syndrome is a left tactile anomia. Without the aid of vision, patients with tactile anomia are unable to name an object placed in their left hand. Yet, they are still able to

Abbreviations: BA, Brodmann area; CC, corpus callosum; CD, callosal dysgenesis; fMRI, functional magnetic imaging; LI, laterality index; ROI(s), region(s) of interest; S1, primary somatosensory cortex; S2, secondary somatosensory cortex.

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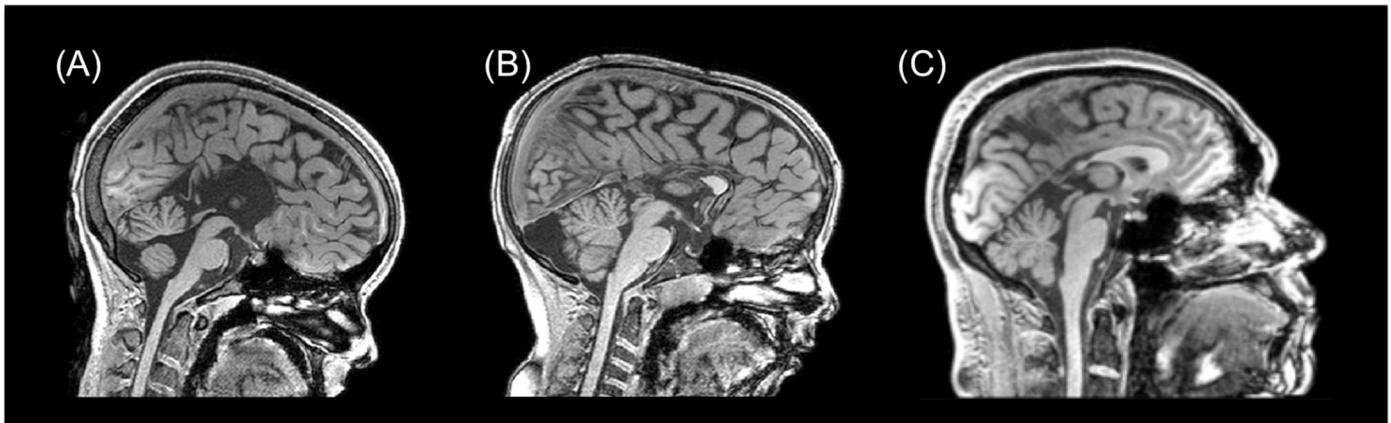


Fig. 1. Sagittal slices showing the anatomical types of callosal dysgenesis that took part in this study: (A) agenesis ($N = 2$), (B) partial agenesis ($N = 2$), and (C) hypoplasia ($N = 2$).

recognize the objects that they cannot name by touch; that is, they do not necessarily suffer from tactile agnosia. For example, the patient reported on by Yamadori et al. (1980) suffered an embolic stroke in the superomedial anterior surface of the right hemisphere including the CC. He showed a severe impairment in naming objects placed in his left hand; however, tactile recognition with the left hand could be easily demonstrated by his ability to pantomime the use of the objects that he had just been unable to name, or to pick with his right hand an object that he inspected with the left out of an array of five alternatives. In the patient reported on by Veronelli et al. (2014), a left tactile anomia was caused by a hemorrhagic stroke that destroyed the cortex and sub-cortex of the right postcentral and supramarginal gyri. In this case, tactile anomia was secondary to an impairment of tactile object recognition with the left hand, that is, to a left tactile agnosia.

The differentiation of tactile naming from tactile agnosia is particularly relevant for the study of CD because of the implications of left tactile object naming for the access of somatosensory information to the language-dominant hemisphere (Endo et al., 1992). In callosotomized patients, information from the left hand, which is conveyed to the somatosensory cortices of the right hemisphere through the spinothalamic-medial lemniscus system, does not gain access to the speech-dominant left hemisphere (Knecht et al., 2000), thus precluding tactile naming (Sperry et al., 1969). Neuroimaging and neurobehavioral studies have shown that the axons that mediate the right-to-left transfer of information between homotopic somatosensory cortices traverse the posterior segment of the CC body (Balsamo et al., 2008; Fabri et al., 1999, 2001, 2005; Ihori et al., 2000; Lassonde et al., 1991; Sperry, 1969). This leftward transfer is a critical step in the sequential processing of tactile information that ultimately leads to tactile naming through parietotemporal connections (Beauvois et al., 1979).

1.3. Solutions to the CD-split-brain paradox: hemispheric symmetry of language, symmetry of the spinothalamic-medial lemniscus pathways, or both

One possibility why patients with CD perform normally on tactile naming is that speech may not be as lateralized in CD patients as in most humans; this hypothesis lacks consistent evidence (Pelletier et al., 2011; Riecker et al., 2007). In this case, the hands of patients with CD would be represented in the somatosensory cortices to equivalent degrees in each hemisphere; both hands would then have access to the language-dominant hemisphere, thus explaining their normal tactile naming ability. Most studies to date have not supported this possibility either (Lum et al., 2011; Reddy et al., 2000). These possibilities are not mutually exclusive, since a gradient of asymmetry of the cortical as well as of the long projection systems seems to be the rule both in normal people and in patients with CD (Geffen et al., 1994).

1.4. Aim of the present investigation

The present investigation aimed to test the possibility that the palm of each hand is bilaterally represented in the cerebral hemispheres, more particularly in the primary (S1) and secondary (S2) somatosensory cortices. To this end, we used functional magnetic resonance imaging (fMRI) to assess the cheirosensory [from the Greek *chéiri* ($\chi\acute{\epsilon}\rho\iota$) = hand] cortical responses to unilateral exteroceptive hand stimulation in patients with CD.

2. Patients, materials and methods

2.1. Characteristics of patients and controls

Six patients with CD without major associated malformations (age = 19 ± 3 years; 4 males) and 12 normal controls (age = 16 ± 5 years; 7 males) participated in the study. All participants were right-handed with the exception of patient CD 6, who was left-handed. Two controls were enrolled for each patient to ensure statistical power to our analyses. Exclusion criteria were a history of neurological disorders for controls, and age below 6 years or MRI contraindication for all participants. Conventional MRI (FLAIR, T1- and T2-weighted images) showed no abnormalities in the brains of controls. The callosal abnormalities were classified as total ($N = 2$) or partial ($N = 2$) agenesis, and hypoplasia ($N = 2$) by experienced neuroradiologists based on specific anatomic features of the brain and the corpus callosum on high-resolution T1-weighted images (Barkovich and Norman, 1988; Kendall, 1983). Other typical features of CD in our patients included parallel and enlarged lateral ventricles, downward displacement of the cingulate gyrus, and radial sulci on the medial hemispheric surface (Fig. 1). All participants and their parents signed a written informed consent before enrollment in the study, which was approved under protocol 225/11 by the Ethics Committee of our institution, (Declaration of Helsinki, 2000).

2.2. Neurological and neurobehavioral assessment

Patients and controls underwent neurological and neuropsychological exams which have been detailed in a previous publication (Tovar-Moll et al., 2014). For the purposes of the present communication, we report the performance of participants on the Tactile Object Naming Test, which was originally designed for the elicitation of tactile left-hand anomia. On this test participants are asked to name a set of 10 common objects placed in each hand at a time without the aid of vision. They are not shown the objects before the test (Fig. 2). Split-brain patients dramatically fail when they carry out the procedure with the left hand, while their right hand performance is flawless. Because patients with CD do not present a split-brain syndrome, we expected that the

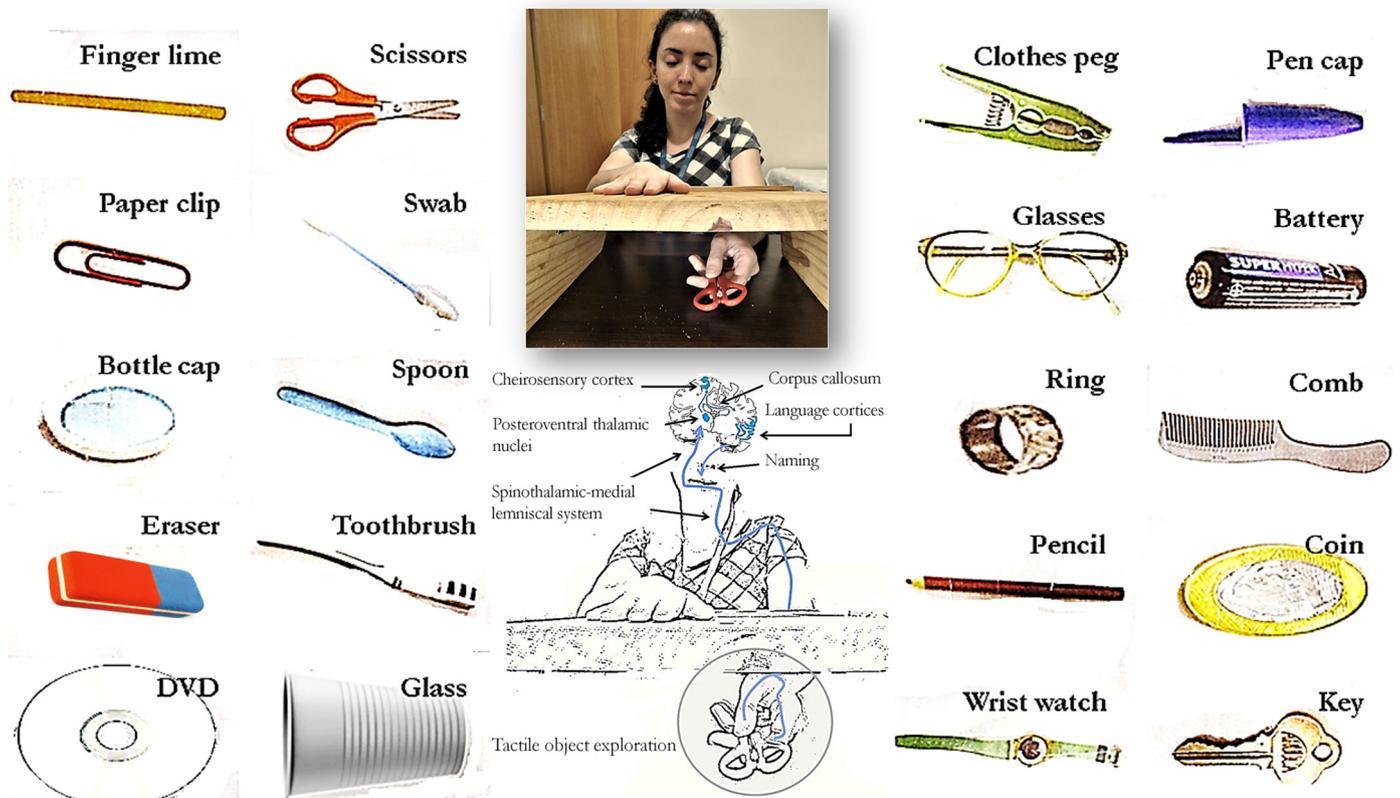


Fig. 2. Somatosensory activation in patients with CD (top) and controls (bottom) in response to unilateral exteroceptive hand stimulation. Activations in (a) and (b) are significant at $p < .05$, familywise error, corrected. Coordinates and activations plotted on the Montreal Neurological Institute standard brain. Color bar represents t -values of activations. L: left; R: right.

Table 1

Demographic characteristics and performance of patients with callosal dysgenesis (CD) and normal controls (NC) on the Tactile Object Naming Test.

Case ID	Type of CD	Sex ^a	Age ^b	Education ^c	Handedness ^d	Edinburgh Inventory ^e	Tactile Object Naming		Barthel ^h Mahoney and Barthel, 1965	TSI ⁱ
							Right hand ^f	Left hand ^g		
CD 01	Hypoplasia	M	39	11	Right	100	10	10	100	23
CD 02	Hypoplasia	M	14	03	Right	100	08	08	090	23
CD 03	Partial agenesis	M	16	07	Right	080	09	10	100	23
CD 04	Partial agenesis	M	12	03	Right	100	10	09	100	23
CD 05	Agenesis	F	10	01	Right	100	10	10	100	23
CD 06	Agenesis	F	17	05	Left	-100	10	09	090	24
NC 01	Normal	F	13	04	Right	080	10	10	100	23
NC 02	Normal	F	08	01	Right	100	10	09	100	23
NC 03	Normal	M	14	07	Right	100	10	10	100	23
NC 04	Normal	M	11	03	Right	100	09	09	100	23
NC 05	Normal	F	09	02	Right	100	-	-	100	23
NC 06	Normal	M	10	04	Right	100	-	-	100	23
NC 07	Normal	M	12	06	Right	60	10	10	100	23
NC 08	Normal	F	16	10	Right	100	-	-	100	23
NC 09	Normal	F	16	08	Right	100	10	10	100	23
NC 10	Normal	M	13	05	Right	100	-	-	100	23
NC 11	Normal	M	37	16	Right	080	10	10	100	23
NC 12	Normal	M	39	11	Right	100	-	-	100	23

a F: female patient; M: male patient $\chi^2 = 0,18, p > .73$
 b CD = 13 ± 3 NC = 17 ± 10 $U = 29, p > .54$
 c CD = 3.5 ± 2.3 NC = 6.8 ± 4.0 $U = 17, p > .08$
 d Based on the hand used for writing, drawing, or both. Normal Values* Range of Possible Scores
 e CD = 63 ± 80 NC = 93 ± 13 $U = 32, p > .75$ ± 100 ± 100
 f CD = 9.5 NC = 9.9 ± 0.4 $U = 16, p > .53$ ≥ 9 0-10
 g CD = 9.3 NC = 9.7 ± 0.5 $U = 15, p > .44$ ≥ 9 0-10
 h CD = 97 ± 5 NC = 100 ± 0 $U = 24, p > .29$ = 100 0-100
 i Test of Severe Impairment (Albert and Cohen, 1992):
 CD = 12 ± 0.4 NC = 23 ± 0 $U = 30, p > .62$ ≥ 23 0-24

* Calculated with the $N = 1$ statistics (Crawford et al., 2010) from the normative databank of the authors (RO-S and JM).

performance of our patients on this test would be normal with either the left or the right hand. Table 1 presents demographic and behavioral characteristics of patients with CD and controls together with other results that might influence their performance on the Tactile Object Naming Test. Categorical variables were statistically analyzed with the χ^2 statistic, while the significance of differences on dimensional variables between groups were assessed with the Mann-Whitney (*U*) statistic. A threshold (α) of 0.05, two-tailed, was adopted for all comparisons unless stated otherwise. Overall, there were no statistical differences between groups on these tests and inventories. As expected, a lack of significant differences on the Tactile Object Naming Test between CD and controls endorsed the absence of a split-brain syndrome in our cases.

2.2.1. Tactile stimulation procedure

To ensure uniformity from one case to the other the same researcher (MM) personally supervised each step of the study protocol in all volunteers. Tactile stimulation consisted in gently rubbing the palm of one hand at a time with a brush with soft bristles while the non-stimulated hand was kept in a comfortable position as still as possible. The examiner executed back and forth movements at a pace of 2 strokes per second parallel to the long axis of the palmar surface between the wrist and tip of the middle finger. Care was taken to maintain a steady contact throughout the range of stimulation.

2.2.2. Neuroanatomical rationale for the palmar stimulation used in the present study

We used Brodmann's area(s) [BA(s)] to chart the regional cortical activations elicited by palmar stimulation (Zilles, 2012). Regardless of modern views, which have shown that S1 sensu stricto is made up of BA 3b only, or "S1 proper" (Kaas, 1983), we did not attempt to pinpoint differential activations in these four areas. Accordingly, we defined the primary somatosensory cortex, or S1, as BAs 3a and 3b, 1 and 2. Cutaneous (exteroceptive) receptors are mainly represented in areas 3b and 1, proprioceptive receptors (muscle spindles) are chiefly represented in areas 3a and 2. Areas 3a and 3b, 1 and 2 sustain independent and chiefly contralateral representations of the body surface (Mai and Forutano, 2012). The secondary somatosensory cortex, or S2, lies in the parietal operculum at the base of the postcentral gyrus deeply extending into the Sylvian fissure; it corresponds to parts of BAs 40 and 43.

The callosal connections of the somatosensory cortices play a critical role in a number of higher-order cognitive processes, among which left tactile naming stands as the most representative. Neuroimaging and neurophysiological studies have shown that the CC mediates interhemispheric transfer between homologous S1 subareas and S2 (Eickhoff et al., 2008, 2012; Nihashi et al., 2005; Schnitzler et al., 1995) Callosal transmission is indicated, for example, by the smaller magnitude of ipsilateral somatosensory activation in normal volunteers (Hansson and Brismar, 1999). The interhemispheric transfer of somatosensory information is supposed to complement the ipsilateral projections from the hands to S1, which are now accepted by most investigators as critical for actions in which the hands work in concert, for left tactile naming, for affective touch, and for object recognition through active touch (Sutherland, 2006). In normal volunteers, bilateral S2 activation during unilateral somatosensory stimulation (Hari et al., 1983; Polonara et al., 1999) is thought to reflect callosal transfer, since ipsilateral activation is delayed compared to the contralateral homotopic areas (Fabri et al., 1999).

To summarize, beginning in BAs 3a (proprioceptive) and 3b (exteroceptive), the somatosensory areas are sequentially connected in a way that the receptive fields of their feature-extracting neurons become progressively more complex as information proceeds from BA 3 (elementary features, such as two-point discrimination) → BA 1 (shape discrimination) → BA 2 (texture discrimination) → BAs 40/43 (tactile object recognition) → (via CC) → language cortex.

2.2.3. Mechanical and neurophysiological characteristics of the palmar stimulation used in the present study

The tactile stimulation employed in the present study was essentially a passive one, that is, the subjects played no active role in the generation of somatosensory activity. Passive somatosensory stimulation has a long history in clinical and experimental neurology (Landry, 1852). Its neural underpinnings have been extensively investigated since the nineteenth century (Freeman and Orkun, 2002). Our stimulation procedure ensured that rapidly adapting cutaneous receptors were stimulated with minimal contamination from skin stretching (slowly adapting Ruffini endings and Merkel disks), active movement, or proprioceptive stimulation (Dellon, 1978). The cutaneous stimulus thus generated was well-suited to activate BA 3b in the posterior bank of the central sulcus, BA 1 (rapidly adapting receptors) in the shoulder and crown of the contralateral postcentral gyrus, and BA 2 in the postcentral sulcus (Lent, 2010). This area is a convergence zone for BAs 3b and 1, thalamocortical extero- and proprioceptive afferents, and for the homologous area 2 through callosal projections (Moll and de Oliveira-Souza, 2017).

In normal right-handed volunteers, a stimulus protocol similar to the one employed in the present study elicited activations in the left (contralateral) areas 3b and 1, and bilaterally in a region of the parietal operculum that corresponds to S2 (Bodegård et al., 2000). This pattern of cortical activation concurs with the predominantly exteroceptive stimulus used in that study and with the predominant exteroceptive role of BAs 3b and 1.

2.3. Neuroimaging

2.3.1. Study design

All subjects underwent a 3 T magnetic resonance scanner image acquisition protocol (Achieva, Philips Medical Systems), which included the following anatomical sequences: T1-weighted volumetric sequence (TR/TE/matrix/FOV/slice thickness: 7.2 ms/3.4 ms/240 × 240/240 mm/1 mm thick), turbo spin-echo-weighted T2 axial plane (TR/TE/matrix/FOV/slice thickness = 3884 ms/120 ms/308 × 303/232 mm/2.5 mm), and FLAIR images in the axial plane (TR/TE/TI/matrix/FOV/slice thickness/GAP = 1000 ms/125 ms/2800 ms/ 288 × 168 / 230 (AP), 182.0833 (RL) mm / 4.5 mm / 1.0 mm). A block design was used, and functional images were acquired using a T2*-weighted echoplanar (TR/TE/matrix/FOV/slice thickness: 2000 ms / 22 ms / 80 × 80 / 240 mm × 240 mm / 3 mm). Each run (one for the right and another for the left-hand stimulation) consisted in 10 alternating blocks of hand stimulation x rest lasting 10 volumes each were repeated five times totalizing 100 volumes. Each run lasted 200 s.

2.3.2. Neuroimaging data processing and analysis

All images were anonymized and visually inspected for artifacts before analysis. fMRI data related to the left-hand activations of one control subject (NC 4) were excluded due to movement artifacts. Functional images were analyzed using Statistical Parametric Mapping (SPM8 www.fil.ion.ucl.ac.uk/spm/software/spm8) implemented in Matlab R (The Mathworks INC; <http://www.mathworks.com/>) \t "_blank (Friston et al., 1995; Worsley and Friston, 1995). The standard two pass realign to mean procedure of SPM was used and then slice time correction was applied. Functional images were co-registered and normalized to the standard Montreal Neurological Institute (MNI) EPI template using 25 non-linear frequency cutoff normalization. The voxel dimensions of each reconstructed functional scan were 3 mm × 3 mm × 3 mm. Functional images were also spatially smoothed using a 6 mm full-width half-maximum Gaussian spatial kernel. Unwanted low frequencies in the fMRI time-series were removed with high-pass filtering (128 s) and cubic detrending (Macey et al., 2004).

In the first level analysis, pre-processed images of both runs of each participant were analyzed with a General Linear Model comprising 2

predictors: rest and tactile stimulation for the right or the left hand. Predictors were modeled as a boxcar function with a length of 20 s for Rest and 20 s for Tactile Stimulation convolved with canonical hemodynamic response function (Zarahn et al., 1997). In the first level analysis, categorical contrasts were generated for Tactile Stimulation vs. Rest for each run. Within- and between-group comparisons were performed using a fixed effect analysis.

Significant brain activations were reported using either uncorrected ($p < .001$ and a minimum cluster level of 5 voxels) or voxel-level familywise error correction over the whole brain ($p < .05$, corrected for multiple comparisons). Small volume correction was performed using predefined region(s) of interest [ROI(s)] created using the SPM8Anatomy toolbox.

2.3.3. Laterality index

A laterality index (LI) was calculated for each group based on the random effects group analysis using the activated voxels in response to stimulation of the right or the left hand in the selected ROIs ($p < .05$, familywise error corrected for multiple comparisons at cluster level). LIs were computed according to the usual formula (Oldfield, 1971; Seghier, 2008): $LI = (R-L)/(R + L)$. LI values may range from -1 (strongly left-lateralized) to $+1$ (strongly right-lateralized).

3. Results

Whole-brain analyses revealed distinct patterns of cortical somatosensory responses to unilateral passive tactile stimulation for each group. Thus, while tactile stimulation in controls engaged S1 and S2 bilaterally, in the patients it was restricted to contralateral S1 and S2 for

both hands (Fig. 3 and Supplementary Figure). The cluster centroid coordinates (voxel maxima) for each group are shown in Table 2.

A direct comparison between controls and patients revealed increased bilateral activation in S1 and S2 in controls (Fig. 4); the opposite contrast did not show suprathreshold activations (Table 3). These findings are consistent with LI values for each hand in controls and in patients (Table 3 and Fig. 4).

4. Discussion

4.1. Main findings of the present study

The main findings of the present study were (i) the absence of ipsilateral somatosensory activation in response to an exteroceptive nonpainful moving stimulus applied to the medial surface of the palm of each hand in patients with CD (Table 2), (ii) the overall lesser degree of activation in CD in comparison to controls (Tables 2 and 3, and Figs. 3 to 5 and supplementary), and (iii) the sparing of tactile naming in patients with CD with either hand, but especially the left, thus confirming the absence of a full-blown disconnection syndrome in them. The ipsilateral lack of activation in our patients supports the concept of a “core syndrome” of callosal agenesis (Brown and Paul, 2019); likewise, the absence of a classical disconnection syndrome, which makes up the core of the CD-split-brain paradox, concurs with the literature (Lassonde et al., 1991; Saul and Sperry, 1968). However, they fail to explain the phenomenon in ways that would fit current conceptual frameworks (Section 1.1).

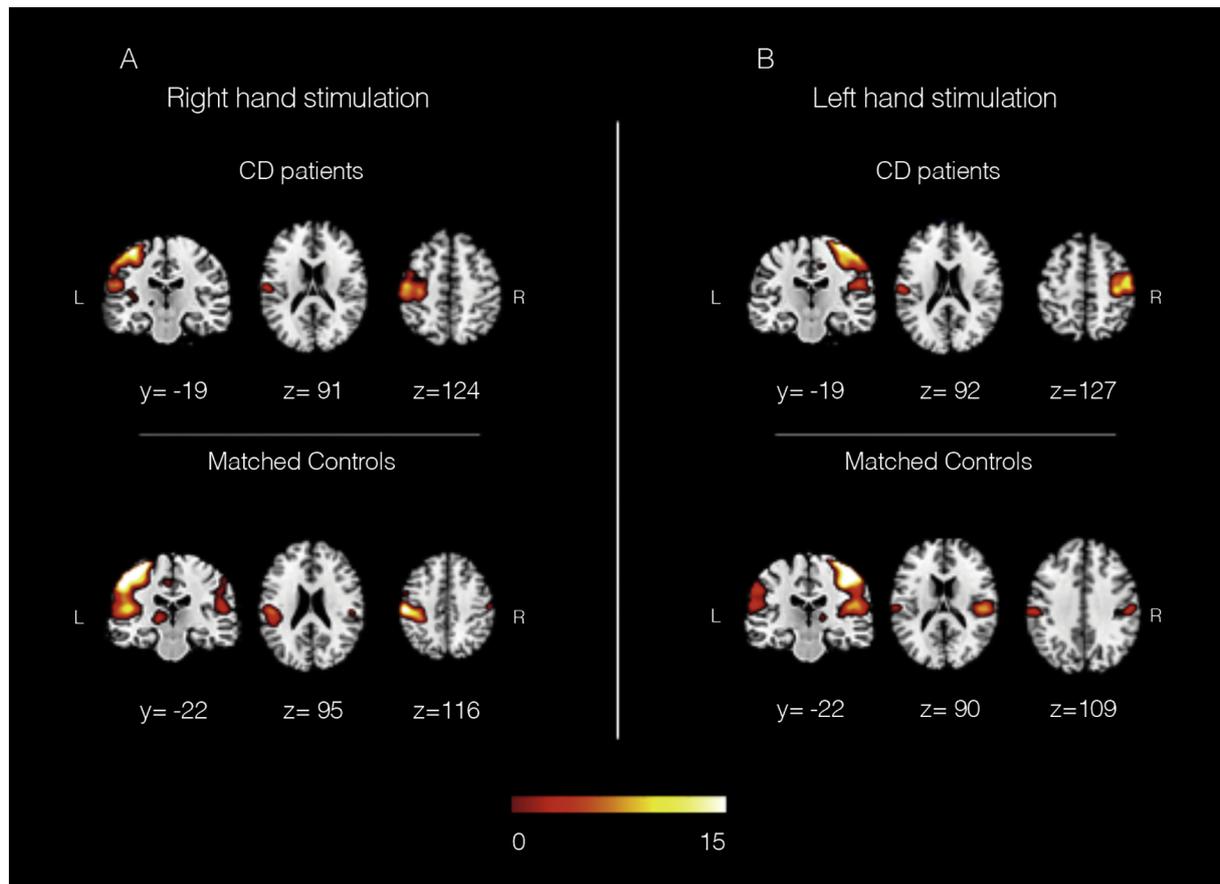


Fig. 3. Increased brain activation in controls when compared to CD patients in response to unilateral exteroceptive hand stimulation. Activations in (a) and (b) are significant at $p < .001$, cluster size of 5 voxels. Coordinates and activations plotted on the Montreal Neurological Institute standard brain. Color bar represents t -values of activations. L: left; R: right.

Table 2
Somatosensory activation in controls and patients with callosal dysgenesis in response to unilateral tactile stimulation of the hands^a.

Region	Side	Brodmann area	Cluster size	LI	MNI ^b			Z-score
					x	y	z	
Controls								
<i>Stimulation of Right Hand</i>								
S1	Left hemisphere	1	545	-0.70	-39	-34	64	21.97
	Right hemisphere	1	056		-57	-16	46	06.86
			1	039		-45	-34	52
S2	Left hemisphere	1	321	-0.51	-48	-22	16	10.84
	Right hemisphere	40	104		-54	-25	16	06.97
<i>Stimulation of Left Hand</i>								
S1	Left hemisphere	40	051	-0.82	-54	-22	40	06.18
	Right hemisphere	1	508		-42	-28	64	25.24
S2	Left hemisphere	40	084	-0.36	-63	-25	22	06.00
		6/1	039		-48	-07	07	05.71
	Right hemisphere	40	259		-51	-22	22	09.16
Callosal Dysgenesis								
<i>Stimulation of Right Hand</i>								
S1	Left hemisphere	1	347	-1.00	-36	-34	67	14.96
		4/1	015		-63	-10	28	06.28
	Right hemisphere	-	000		-	-	-	-
S2	Left hemisphere	1	079	-1.00	-54	-19	22	08.11
	Right hemisphere	-	000		-	-	-	-
<i>Stimulation of Left Hand</i>								
S1	Left hemisphere	-	000	-1.00	-	-	-	-
	Right hemisphere	1	246		-48	-19	58	11.90
S2	Left hemisphere	-	000	-1.00	-	-	-	-
	Right hemisphere	40	106		-54	-19	22	07.14

^a L: left; LI: laterality index; R: right; S1: primary somatosensory cortex; S2: secondary somatosensory cortex.

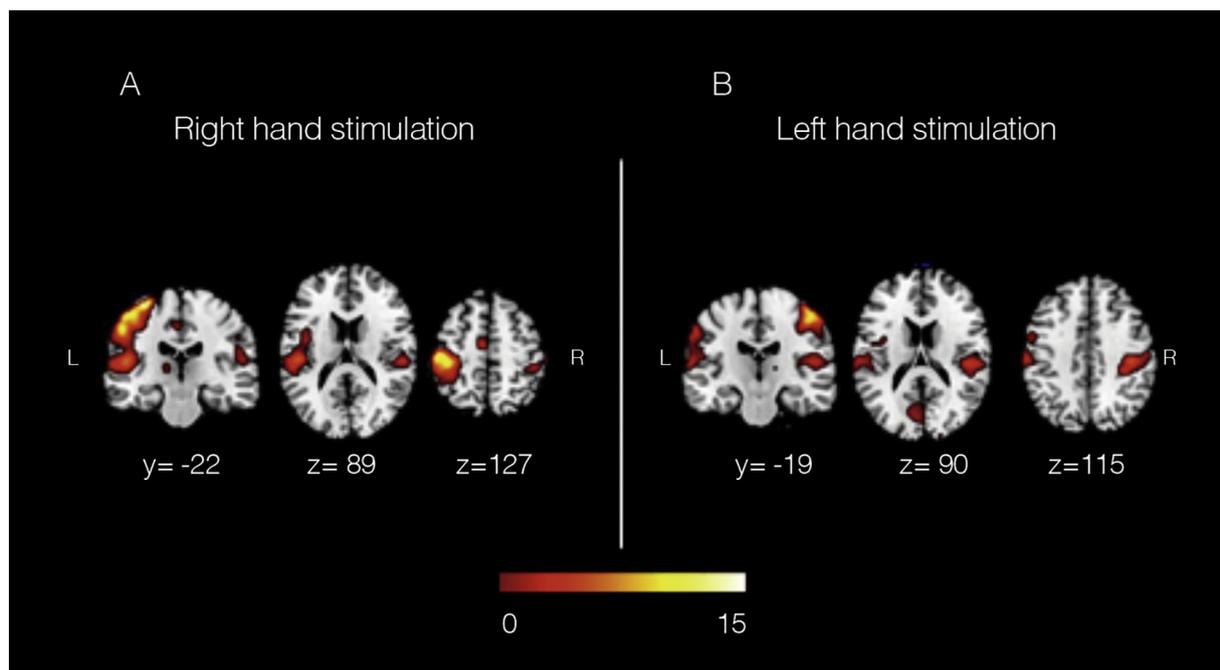


Fig. 4. Laterality indexes based on number of activated voxels ($p < .05$, familywise error corrected for multiple comparisons at cluster level) may range from -1 (fully left-lateralized) to $+1$ (fully right-lateralized).

4.2. The CD-split-brain paradox lingers on

Assuming that the CC plays a directive role in the establishment of the major interhemispheric asymmetries (Chiarello, 1970; Smith, 1945), its congenital absence or maldevelopment should result in a corresponding increase in the hemispheric symmetry of cognitive (e.g., language, praxis) and sensorimotor functions. Ambidexterity, reduced

right ear advantage on dichotic listening, and slower interhemispheric reaction times are commonly cited as evidence for the relative hemispheric autonomy in CD, but they are not prevalent in such cases (Ocklenburg et al., 2015).

4.2.1. Bilateral representation of language in the cerebral hemispheres

Notwithstanding its plausibility (Section 1.3), research has so far

Table 3
Somatosensory activation in controls compared to patients with callosal dysgenesis in response to unilateral tactile stimulation of the hands^a.

Region	Side	Cluster size	Brodmann area	MNI ^b			Z-score
				x	y	z	
Stimulation of Right Hand							
S1	Left hemisphere	440	1	-51	-22	55	12.34
	Right hemisphere	023	1	-57	-16	46	05.28
		067	40	-45	-34	38	04.67
S2	Left hemisphere	210	40	-51	-22	13	07.91
	Right hemisphere	052	40	-54	-25	16	05.87
Stimulation of Left Hand							
S1	Left hemisphere	037	1	-60	-19	40	05.44
	Right hemisphere	344	1	-42	-31	64	16.32
S2	Left hemisphere	118	1	-63	-19	13	05.75
	Right hemisphere	123	40	-54	-25	13	07.06

^a L: left; R: right; S1: primary somatosensory cortex; S2: secondary somatosensory cortex.

^b Montreal Neurological Institute (MNI) coordinates for significant activation maxima of clusters in the group analyses ($p < .05$, familywise error corrected for multiple comparisons at cluster level).

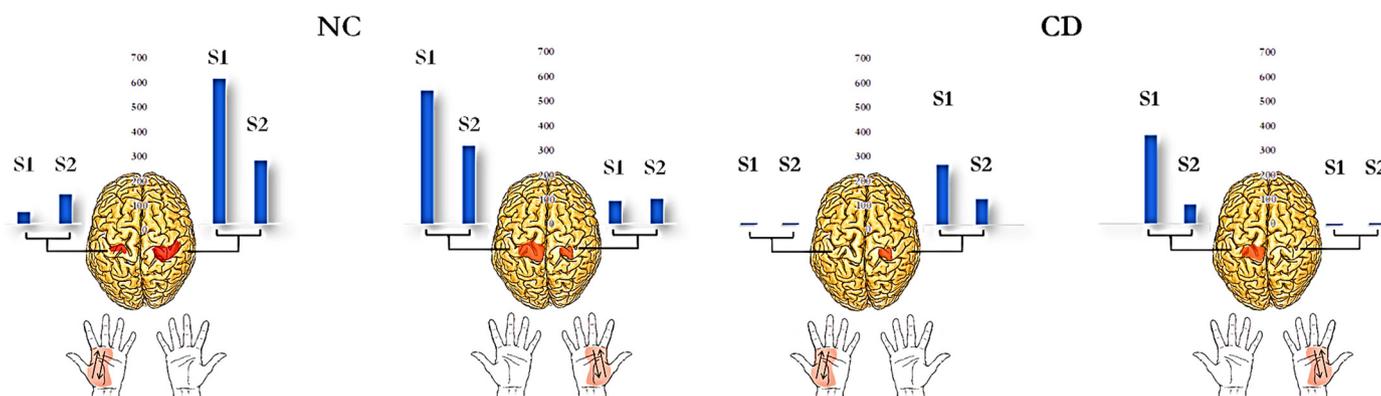


Fig. 5. MNI: Montreal Neurological Institute coordinates for significant activation maxima of clusters in group analyses ($p < .05$, familywise error corrected for multiple comparisons on the cluster level). Cheirosensory cortical engagement in patients with CD differed from that of controls in their overall lower level of activation and because they were exclusively contralateral

been inconclusive in support of a bilateral representation of language in CD. Single case reports using fMRI, the Wada test, magnetoencephalography, or ¹⁸F-DG-PET have indeed demonstrated a symmetrical or even higher right hemisphere representation of oral expressive and receptive language functions in patients with CC agenesis (Hinkley et al., 2016; Kessler et al., 1991; Komaba et al., 1998; Riecker et al., 2007). However, when patients with CC agenesis were compared to a normal group matched for sex, age, and IQ, no differences were detected (Pelletier et al., 2011). Since the issue of language representation in CD falls outside the scope of the present study, we shall not pursue it further.

4.2.2. Hypothesis probed in the present study: the cortical representation of the spinothalamic-medial lemniscus system is symmetric in CD

The medial lemniscus is formed in the lower medulla by the decussation of the fibers originating in the gracile and cuneatus nuclei which, in turn, represent the end station of the sensory axons that run in the dorsal columns of the spinal cord. From the upper pons upwards, the medial lemniscus and the spinothalamic tract ascend together on their way to the posteroventral thalamus, where they terminate on the thalamocortical neurons that project to the sensory cortices (Kaas, 2012). They comprise a collection of fibers which convey extero- and proprioceptive somatosensory information of the contralateral body to the ventral posteroventral thalamic nucleus, which, in turn, is the main source of projections to S1 and S2 (ten Donkelaar et al., 2011). In humans, most fibers of the spinothalamic tract and virtually all fibers of the medial lemniscus project to the contralateral hemisphere (Marani and Schoen, 2005), an arrangement that resembles the well-known

anatomical asymmetries of the human pyramidal tracts (de Oliveira-Souza, 2015). The spinothalamic-medial lemniscus is the critical fiber system for the mediation of active touch and tactile object recognition (Srinivas and Ogas, 1999). The asymmetry of the spinothalamic-medial lemniscal system is the reason why previously normal callosotomized and CC-injured individuals lose the ability to name objects placed in their left hands. In normal individuals, the left spinothalamic-medial lemniscus, which convey tactile information from the left hand, project to the right cheirosensory cortices; therefore, left tactile naming depends on the CC to reach the left, language-dominant, hemisphere (Section 2.2.2). Several lines of evidence agree that the somatosensory transfer that allows tactile naming depends on the integrity of the posterior portion of the CC body (Balsamo et al., 2008; Fabri et al., 1999, 2001, 2005; Ihori et al., 2000; Polonara et al., 2015), which is traversed by the commissural axons of the somatosensory cortices (Caminiti et al., 2013). This callosal segment was absent in four patients of our series and hypoplastic in two.

Notwithstanding the small size of our sample, the contralateral somatosensory representation of each hand survived multiple statistical comparisons and remained robust in all, including the two patients with callosal hypoplasia. Despite the absence of an ipsilateral representation of the hands in the somatosensory cortices, the performance of our patients was flawless on tactile naming as well as on other tasks requiring interhemispheric communication (Tovar-Moll et al., 2014). This finding is in line with the CD-split-brain paradox; however, the absence of ipsilateral somatosensory activation is more akin to what happens in adult callosotomized patients; that is, callosotomized patients show

both tactile anomia and abolition of ipsilateral somatosensory activation. This finding indicates that the CC may not be the only possible pathway for the interhemispheric transfer of tactile naming, but it is certainly necessary for the ipsilateral somatosensory activation in response to tactile stimulation.

The above assertions should be interpreted with caution due to at least two caveats. First, the extreme left-handedness of patient CD 6 might have confounded our results. However, we do not believe that this was the case because the results of the main analyses did not qualitatively change after exclusion of this patient. Second, the small number of CD cases enrolled in the present study may constrain the generalization of our findings. This, in fact, is a limitation of most studies of rare diseases, in which an optimum trade-off should be sought between the goals of the study and the patients' motor and cognitive skills. We attempted to circumvent some of these limitations by including only patients with "pure" CD, i.e., cases of CD not associated with other gross malformations of the nervous system. The kind of experiments that are usually set for investigations like the present one require active engagement of participants. Thus, patients with multiple malformations had to be left out owing to severe motor and cognitive deficits that might have hindered and even precluded the conduction of functional neuroimaging studies.

4.2.3. Cortical representation of the spinothalamic-medial lemniscus system in callosal dysgenesis: fully asymmetric

A less explored possibility proposes that patients with CD have a bilateral representation of the hands in the sensorimotor cortices, thus giving access of both hands to the language-dominant hemisphere, whether the right or the left. Our results do not lend support to this hypothesis; quite on the contrary, patients with CD showed a pattern of exclusive contralateral S1 and S2 activation during stimulation of each hand, while controls showed bilateral, albeit asymmetric, activations of these regions under similar conditions, a finding which was well summarized by their LIs.

4.2.4. A fourth alternative: aberrant interhemispheric pathways

So far, our findings do not support the three most popular solutions to the CD-split-brain paradox, namely, (i) bilateral hemispheric representation of language, (ii) bilateral hemispheric representation of the spinothalamic-lemniscal system (this study), and (iii) a variable combination of (i) and (ii). A fourth alternative, which has indeed been entertained since the early twentieth century (Probst, 1901), could not until recently be probed in vivo due to technical limitations. This alternative, which also draws on neuroplasticity, has gained increasing support from in vivo neuroimaging studies. Accordingly, the inductive role exerted by CD on brain architecture at specific epochs of neural development ultimately leads to the formation of interhemispheric pathways which are not usually present in normal, i.e., CC-eugenic, individuals (Jakab et al., 2015; Tovar-Moll et al., 2007, 2014; Wahl et al., 2009). This proposal is consistent with the rearrangement of the structural connectome (Meoded et al., 2015; Owen et al., 2013) and with the preservation of the microstructure and asymmetries of the major white matter bundles in CD (Bénézit et al., 2015). More to the point, our patients' normal performance on left tactile naming was probably mediated by the previously described aberrant bundles interconnecting the posterior parietal cortices (Tovar-Moll et al., 2014). These alternative routes might take upon the normal role of the CC in the right-to-left transfer of cheirosensory information, thus allowing tactile naming to be normally performed.

To summarize, cheirosensory information was highly lateralized in our patients with CD who showed no evidence whatsoever of a classical disconnection syndrome as clinically expressed by left hand anomia. Our findings weaken the bilateral somatosensory representation hypothesis as an explanation for the sparing of left tactile naming in our patients. The paradoxical sparing of left tactile naming in CD may at least in part be explained by the aberrant interhemispheric bundles

which were recently described in the same patients who took part in the present study (Tovar-Moll et al., 2014).

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Conflict of interest

None to declare.

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