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Research report

Abnormal interhemispheric motor interactions in patients with callosal agenesis

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HIGHLIGHTS

- In controls, unilateral hand movements evoked asymmetric BOLD activity for both M1.
- BOLD connectivity show that this is induced by interhemispheric motor suppression.
- In controls, this suppression was mediated by microstructure of specific CC fibers.
- In acallosal patients interhemispheric motor suppression was absent.

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ABSTRACT

During unilateral hand movements the activity of the contralateral primary motor cortex (cM1) is increased while the activity of the ipsilateral M1 (iM1) is decreased. A potential explanation for this asymmetric activity pattern is transcallosal cM1-to-iM1 inhibitory control. To test this hypothesis, we examined interhemispheric motor inhibition in acallosal patients. We measured fMRI activity in iM1 and cM1 in acallosal patients during unilateral hand movements and compared their motor activity pattern to that of healthy controls. In controls, fMRI activation in cM1 was significantly higher than in iM1, reflecting a normal differential task-related M1 activity. Additional functional connectivity analysis revealed that iM1 activity was strongly suppressed by cM1. Furthermore, DTI analysis indicated that this contralaterally induced suppression was mediated by microstructural properties of specific callosal fibers interconnecting both M1s. In contrast, acallosal patients did not show a clear differential activity pattern between cM1 and iM1. The more symmetric pattern was due to an elevated task-related iM1 activity in acallosal patients, which was significantly higher than iM1 activity in a subgroup of gender and age-matched controls. Also, interhemispheric motor suppression was completely absent in acallosal patients. These findings suggest that absence of callosal connections reduces inhibitory interhemispheric motor interactions between left and right M1. This effect may reveal novel aspects of mechanisms in communication of two hemispheres and establishment of brain asymmetries in general.

1. Introduction

The corpus callosum (CC) is the largest commissure in humans, connecting the two hemispheres via 200–350 million axon fibers [1]. Callosal fibers mostly project excitatory on pyramidal neurons of the homotopic contralateral area, which then often activate GABAergic interneurons in the contralateral hemisphere [2]. Thus, the ultimate effect of callosal activity on the contralateral hemisphere is assumed to be mostly inhibitory [2]. A domain where transcallosal inhibition is important is motor control of hand movements. During intended unilateral hand movements there is an asymmetric involvement of the primary motor cortex (M1) in the two hemispheres. Due to the architecture of the motor system there is a predominant role of the contralateral M1 (cM1) in controlling the hand [3,4]. The contributions of the ipsilateral M1 (iM1) are more complex and show only an initial involvement [5]. Previous TMS/MEP studies indicate that iM1 can control the ipsilateral hand,

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most likely through uncrossed corticospinal projections [3–6]. This initial ipsilateral control is normally inhibited soon through trancallosal inhibition by the cM1 in conditions where crosstalk is obstructive [4,6–8]. Functional magnetic resonance imaging (fMRI) studies have revealed concordant asymmetric involvements of both M1s for hand movements. During unilateral hand movements blood oxygenation level dependent (BOLD) activation of cM1 is increased while the activation of iM1 is decreased or reduced, compared to a baseline period with no motor preparation [9–11]. This asymmetric BOLD activation pattern is potentially caused by a contralateral to ipsilateral M1 motor suppression. Based on an fMRI study in healthy subjects, Hayashi et al. [10] proposed a model that assumes that contralaterally induced ipsilateral BOLD suppression is caused by transcallosal inhibition. In order to test this postulated transcallosal effect we used a multimethod neuroimaging approach in healthy participants and in patients with agenesis of the corpus callosum (AgCC). We first examined interhemispheric motor suppression in healthy participants using a functional connectivity approach. Using the psychophysiological interactions (PPI) method O'Reilly et al. [12], we determined whether suppression of iM1 BOLD activity is dependent on the activity of cM1. Next, by using a novel approach, we then tested for the first time, whether contralaterally induced BOLD suppression of iM1 was related to the microstructural properties of specific callosal fibres as determined with diffusion tensor imaging (DTI). Since previous studies investigating the link between TMS induced interhemispheric motor inhibition and callosal microstructure [13,14], we hypothesized that a strong iM1 BOLD suppression in a healthy individual should be associated with an "efficient" callosal microstructure. In a critical experiment, we than tested in a second approach, whether this contralaterally induced iM1 suppression is absent in patients with AgCC. AgCC is a rare condition, in which callosal fibers are congenitally completely or partially absent, caused by different genetic or environmental factors during prenatal callosal development [15]. As a consequence AgCC patients usually show prolonged visual interhemispheric transfer times [16,17] and deficiencies in different higher cognitive abilities, where interhemispheric integration is important [18,19]. In the motor domain, early TMS studies have demonstrated that interhemispheric motor inhibition is affected in these patients [20,21], therefore, we hypothesized for our patients that the lack of callosal fibers should diminish interhemispheric motor BOLD suppression during unilateral hand movements. This fact would result in a more symmetric involvement of both M1s in AgCC patients. Beyond motor functions, previous work indicates that callosal suppression in healthy individuals is important for establishment of brain asymmetries [22,23]. In AgCC patients, brain asymmetries are reduced [19] or abnormal [24], reflecting hemispheric independence for sensory and cognitive functions.

2. Material and methods

2.1. Participants

Four patients with complete, isolated and one patient with partial AgCC (see Fig. 1) took part in the study (three males; mean age, 27.4 years; range, 18–55 years). All AgCC patients had undergone normal schooling and came from German middle class families. They were recruited via internet advertisements. Two AgCC patients were right-handed, one left-handed and two ambidextrous as measured by the Edinburgh Handedness Inventory [25]. AgCC patients were compared to seven age-, and gender-matched healthy controls (5 males; mean age, 29.8 years; range 18–64 years). Independent t tests revealed that there was no significant group difference in age ($p = 0.80$) and a two-sample Fisher's exact test showed that there was no significant group difference in gender ($p = 0.99$). In order to balance both groups in regard to handedness, four out of seven healthy participants were right-handed and three left-handed as measured by the Edinburgh Handedness Inventory [25]. In order to replicate the findings by Hayashi et al. [10] in a bigger sample of healthy controls, thirty-eight right-handed healthy participants (17 males; mean age 26.63 years; range 22–31 years) were additionally recruited. In total forty-five healthy participants took part in our study. All participants had normal or corrected-to-normal vision and were paid for participation. Written informed consent was obtained from all participants. The experimental procedures were in accordance with the ethical regulations of the Max Planck Society and the study was approved by the local ethics committee of the University Hospital Frankfurt am Main.

2.2. Acquisition of imaging data

All data were acquired at the Brain Imaging Center Frankfurt am Main, Germany, using a Siemens 3-Tesla Trio scanner (Siemens, Erlangen, Germany) with a 8-channel head coil and maximum gradient strength of 40 mT/m.

2.2.1. Anatomical imaging

For co-registration and anatomical localization of functional data, a T1-weighted high-resolution anatomical image of $1 \times 1 \times 1\ mm^3$ was acquired (MP-RAGE, TR = 2250 ms, TE = 2.6 ms, flip angle: 9°, FoV: 256 mm). The acquisition time for the anatomical image was 10 min.

2.2.2. Motor task

For the motor task, a gradient-recalled echo-planar-imaging (EPI) sequence with the following parameters was applied: 36 slices, TR = 2640 ms, TE = 30 ms, flip angle = 90°, FoV = 192 mm, slice thickness = 3 mm, gap thickness = 0.75 mm, voxel size = 3.0 × 3.0 × 3.0 mm. The acquisition time for the motor task was 9 min.

2.2.3. Diffusion tensor imaging

The diffusion-weighted data were acquired using single-shot spin-echo echo-planar imaging (TR = 8200 ms, TE = 99 ms, slice thickness = 2 mm, FoV = 192 mm, voxel size = 2.0 × 2.0 × 2.0 mm, matrix size = 96 × 96). Diffusion weighting was isotropically distributed along 60 directions using a b-value of $1000\ s/mm^2$. Additionally, ten data sets with no diffusion weighting were acquired initially as anatomical reference for motion correction and for computation of diffusion coefficients during the diffusion sequence. To increase signal-to-noise, we acquired three consecutive scans that were subsequently averaged [26]. Total acquisition time for diffusion imaging was 30 min.

2.3. Motor task and experimental procedure

We used a simple visually guided motor task similar as described by Wahl et al. [13]. Stimuli were generated with Presentation® software (Version 10.3, www.neurobs.com) running under Microsoft Windows XP and were back-projected onto a frosted screen with a liquid–crystal-display projector. Participants viewed the screen through a mirror fixed on the head coil. We acquired a total of 192 scans while participants performed four blocks (21 s per condition) of alternating rest, pursing movements of lips, flexion movements of the fingers of the left hand, fingers of the right hand, toes of the right foot, and toes of the left foot. Participants were instructed to perform the movements at a self-paced rate of 1 Hz. Participants were familiarized with the instructions and practiced the motor movement before scanning. After the experiment, all participants confirmed that they had been able to carry out the task correctly.

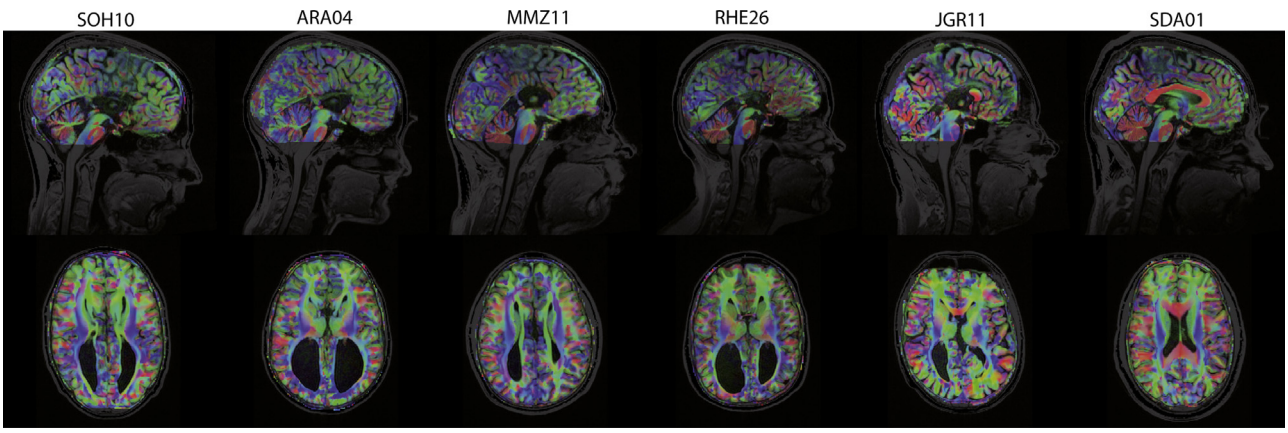

Fig. 1. Sagittal (top) and axial (bottom) view of the DTI-based images overlaid onto the individual's T1-weighted anatomy. The colors represent fiber orientations in different directions: right–left (red), anterior–posterior (green) and superior–inferior (blue). The corpus callosum of the healthy participant SDA01 (right) is clearly visible in red. The images of SOH10, ARA04, MMZ11 and RHE26 demonstrating complete callosal agenesis and JGR11 has partial agenesis where the anterior part of the corpus callosum is still intact. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Throughout the sessions, the motor movements were monitored outside the scanner room by the experimenter.

2.4. Analysis of functional data

2.4.1. Preprocessing

Functional motor data were analyzed using FEAT, part of the FSL toolbox (www.fmrib.ox.ac.uk/fsl). Images were pre-processed using a number of steps: motion- and slice-timing correction, spatial smoothing with a 5 mm FWHM Gaussian kernel, high-pass filter cutoff in seconds (150), linear coregistration to the individual's high-resolution T1-weighted anatomical image and to the standard stereotaxic space template of the Montreal Neurological Institute (MNI).

2.4.2. Atlas-based ROI analyses

In a first step, cortical regions for ROI-based analyses were defined probabilistically using the Jülich Histological Atlas (left hand M1 = Area GM_PMC_4p_L; right hand M1 = Area GM_PMC_4p_L) in MNI space [27]. Second, both M1s were transformed using FLIRT [28] from standard MNI space into the native BOLD space, via the individual's high-resolution anatomical image, to extract the mean amplitude of the BOLD activation in M1. Data from each participant were visually inspected to confirm that the transformation procedure was successful. Since we had only predictions for the interactions of both M1s of the hand area, only the conditions of finger movements for the hands were used for further analyses. Based on *z*-statistic procedures, we used FEAT-QUERY to compute the mean amplitude of the BOLD activation in the left and right hand M1 for each unilateral hand movement compared to baseline. Two *z*-values per hand movement were extracted (ipsilateral M1, contralateral M1). We used these data as input to our second-level statistics, which we performed with SPSS (version 20, SPSS Inc., Chicago, IL, United States of America). For the large sample of healthy participants ($N = 45$) we computed a two-way (2×2) repeated measures ANOVA with hemisphere (ipsilateral M1 = iM1; contralateral M1 = cM1) and hand (dominant; non-dominant) as within-participants factors. For the comparisons between AgCC patients and the subgroup of seven healthy participants we performed a three-way ($2 \times 2 \times 2$) repeated measures ANOVA with hemisphere (ipsilateral M1 = iM1; contralateral M1 = cM1) and hand (dominant; non-dominant) as within-participants factors and group (AgCC patients; healthy participants) as between-participants factors. Statistical tests were performed using an α-level of 0.05.

2.4.3. Functional connectivity

We used the psychophysiological interactions (PPI) approach to determine which voxels in the brain co-vary with a seed region of interest during a particular behavioral task [12], which were unilateral hand movements in our study. As seed regions we used the contralateral M1 hand activity clusters, which we again defined probabilistically from the Jülich Histological Atlas by using the same procedure as mentioned above. Depending on the design of the general linear model (GLM), these covariations between the seed region and all other voxels in the brain could be a negative (a more "suppression"-like) or a positive (a more "facilitation"-like) connectivity pattern. For each individual participant we created four different PPI maps (right hand movement – left (contralateral) M1 activation > whole brain negative connectivity; right hand movement – left (contralateral) M1 activation > whole brain positive connectivity; left hand movement – right (contralateral) M1 activation > whole brain negative connectivity; left hand movement – right (contralateral) M1 activation > whole brain positive connectivity). We used these maps as input to random effects higher-level analyses in FEAT. The random effects analyses were conducted using the FLAME (FMRIB's Local Analysis of Mixed Effects) 1 + 2 option. This analysis was conducted to compare the PPI connectivity pattern of the AgCC patients with those of the seven age- and gender-matched healthy participants. The statistical threshold was set at a FWE-corrected cluster thresholding option with a p value < .05 and Z value >2.3.

In addition to calculating group statistics we also determined a quantitative connectivity value representing the interhemispheric cM1-to-iM1 motor suppression for each individual control. This value was based on *z*-statistic procedures and was computed by using the two negative connectivity PPI maps mentioned above. For each map we extracted a mean *z*-value for the ipsilateral hand M1 area. A higher *z*-value was associated with a stronger cM1-to-iM1 motor suppression. The two *z*-values were averaged for each hand movement and entered as dependent variable in correlation or in multiple-regression analyses.

2.5. Analysis of diffusion data

2.5.1. Preprocessing

Diffusion tensor images were analyzed using FDT (FMRIB's Diffusion Toolbox) implemented in FSL. Preprocessing steps included (i) correction for eddy current and head motion, (ii) correction of the gradient direction for each volume using the rotation parameters from the head motion. For the evaluation of white-matter

microstructure, we calculated fractional anisotropy (FA) maps by using the DTIFIT tool. By using FNIRT all diffusion images were non-linearly aligned to the standard space template of the MNI brain via the individual's high-resolution T1-weighted anatomical image.

2.5.2. Geometry-based tract segmentation in the corpus callosum (CC)

In order to test whether the inter-individual variation of the BOLD interhemispheric motor suppression is related to the individual callosal white-matter microstructure we performed a standardized geometrical parcellation of the CC for all healthy controls. Previous studies used anatomical markers for parcellating the CC into different subregions [29]. In our study, we used a parcellation method that was validated using in-vivo DTI fiber tracking in humans [30]. Here, each callosal segment represents specific fibers projecting to distinct cortical areas. In accordance with the scheme of Hofer and Frahm [30], we measured the mid-sagittal length of the maximum anterior–posterior extent of the whole CC in MNI standard space. As defined by the scheme, the whole CC was divided once into five sub-segments (see Fig. 4a) in MNI standard space. These segments were from anterior to posterior along the *y*-axis: anterior third (I), anterior midbody (II), posterior midbody (III), isthmus (IV) and the splenium (V). Since FA images of all participants were non-linearly aligned to MNI standard space, we used an automatic procedure in transforming the callosal segments back to the FA images of each participant. Finally, we computed for each participant's FA map mean FA values for the five corresponding callosal sub-segments. For regression analyses of the relationship between cM1-to-iM1 interhemispheric motor suppression and callosal white-matter microstructure, the average *z*-value for the cM1-to-iM1 interhemispheric motor suppression mentioned above was entered as dependent variable and the FA values of the different callosal segments were entered as independent variables, either individually or in multiple-regression analyses.

3. Results

3.1. ROI Analyses in the larger control group

To test the inhibitory interhemispheric motor control as described by Hayashi et al. [10], a two-way (2×2) repeated measures ANOVA was computed with hemisphere (ipsilateral M1 = iM1; contralateral M1 = cM1) and hand (dominant; non-dominant) as within-participants factors. The ANOVA revealed a significant main effect of hemisphere ($F_{(1,44)} = 288.08$; $p < 0.001$; $\eta^2 = 0.87$), indicating that participants showed reduced BOLD activity for iM1 (0.10 ± 0.08) compared to cM1 (0.84 ± 0.08) during hand movements (Fig. 2a). Bonferroni corrected post-hoc tests showed this effect was slightly different for both hands: when participants moved their dominant hand, iM1 activity was decreased ($p < 0.001$; Cohen's $d = 1.35$), whereas when they moved their non-dominant hand, the activity was reduced ($p < 0.001$; Cohen's $d = 1.15$) compared to the baseline activity. Additionally, a significant main effect of hand emerged ($F_{(1,44)} = 38.60$; $p < 0.001$; $\eta^2 = 0.47$), indicating that participants had reduced BOLD activity in M1 when they moved their dominant hand (0.35 ± 0.08) in comparison to their non-dominant hand (0.60 ± 0.08). The effect of hemisphere × hand interaction was not significant ($F_{(1,44)} = 0.68$; $p = 0.41$; $\eta^2 = 0.02$). However, Bonferroni corrected post-hoc tests showed that movements with the dominant hand evoked stronger reduction in the iM1 activity than movements with the non-dominant hand ($p < 0.001$; Cohen's $d = 0.52$), whereas the asymmetric activation level in the cM1's was not significant ($p = 0.054$), but showed a strong trend for increased activation during the non-dominant hand movements (Fig. 2a).

3.2. ROI Analyses for AgCC patients and controls

In order to test whether the absence of the corpus callosum reduces inhibitory interhemispheric motor interactions we computed a three-way ($2 \times 2 \times 2$) repeated measures ANOVA with hemisphere (ipsilateral M1 = iM1; contralateral M1 = cM1) and hand (dominant; non-dominant) as within-participants factors and group (AgCC patients; healthy controls) as between-participants factor. The ANOVA revealed a significant main effect of hemisphere ($F_{(1,10)} = 43.61$; $p < 0.001$; $\eta^2 = 0.81$), indicating that participants had a significantly reduced BOLD activity for iM1 (0.82 ± 0.21) compared to cM1 (1.44 ± 0.21) during hand movements as well as a significant main effect of group ($F_{(1,10)} = 7.18$; $p = 0.02$; $\eta^2 = 0.42$), indicating that AgCC patients (1.68 ± 0.32) had an overall higher M1 BOLD activity than controls (0.58 ± 0.27) during unilateral hand movements. Moreover, a significant hemisphere × group interaction emerged ($F_{(1,10)} = 6.23$; $p = 0.03$; $\eta^2 = 0.38$), indicating that AgCC patients had a ten times higher iM1 activity (1.49 ± 0.33) than controls (0.15 ± 0.28, Fig. 2b). Bonferroni-corrected post-hoc tests showed an increased iM1 activity for AgCC patients compared to controls ($p = 0.02$; Cohen's $d = 1.85$), whereas the difference in the activation level of cM1 was not significant ($p = 0.13$) between the groups. The main effect of hand and all other interaction effects failed to reach significance ($p > .49$).

3.3. Functional connectivity for AgCC patients and controls

3.3.1. Negative connectivity

In order to test whether there is a suppression of iM1 during unilateral hand movements we computed a negative PPI connectivity map using cM1 as seed region. For both left and right hand movements we found a strong interhemispheric cM1-to-iM1 motor suppression in healthy participants ($p < .05$, $Z > 2.3$, FWE corrected, Fig. 3a). Interestingly, in addition to the iM1 motor suppression we also found a strong bilateral suppression of the medial portion of the premotor cortex also known as the supplementary motor area (SMA) by the cM1. In contrast, both suppression patterns (cM1-to-iM1 and premotor) were completely absent in AgCC patients (Fig. 3b) and a group difference between healthy participants and AgCC patients revealed only a cM1-to-iM1 interhemispheric motor suppression for healthy participants ($p < .05$, $Z > 2.3$, uncorrected, Fig. 3c).

3.3.2. Positive connectivity

Based on previous studies about interhemispheric motor interactions and the results of the ROI analyses described above we did not expect a positive PPI connectivity between cM1 and iM1 in healthy participants. Analyses showed that there was no interhemispheric cM1-to-iM1 facilitation ($p < .05$, $Z > 2.3$, FWE corrected, Fig. 3d), neither for left nor for right hand movements. Since the AgCC patients showed increased iM1 activation during unilateral hand movements, indicating that in addition to cM1, iM1 is also involved in executing the movement, one could expect that both hemispheres be functionally coupled during hand movements. However, the PPI connectivity analyses did not indicate such a facilitatory cM1-to-iM1 relation, suggesting that also in AgCC patients the two hemispheres execute the hand movements independently from each other (see Fig. 3e–f).

3.4. Functional connectivity and callosal microstructure

The results above indicate that the absence of the corpus callosum nearly completely abolishes the interhemispheric motor

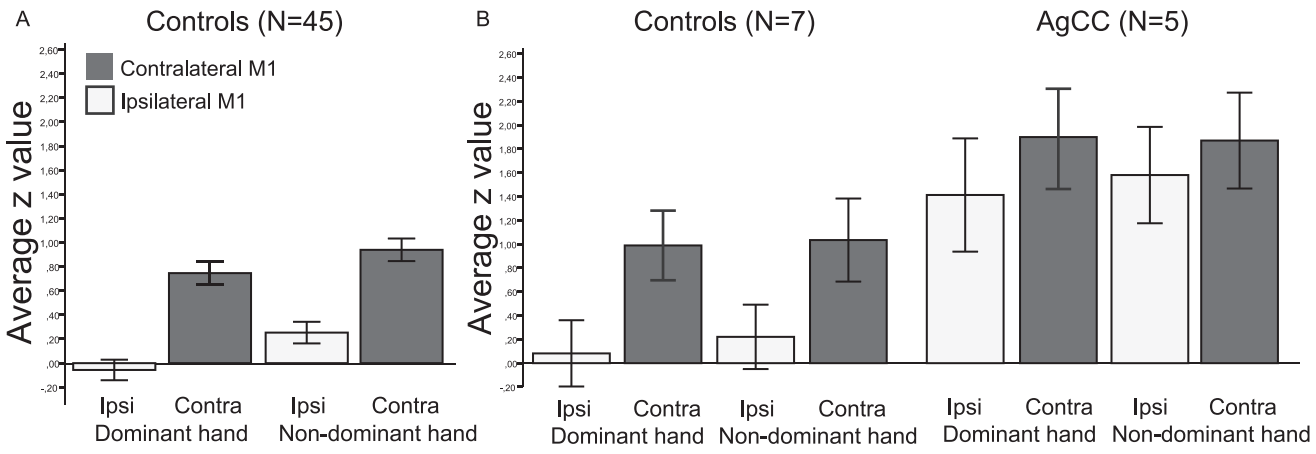

Fig. 2. Ipsilateral and contralateral BOLD responses in M1 during unilateral hand movements. (A) Regions-of-interest (ROI) analysis in forty-five healthy participants indicates an asymmetric BOLD response for the contralateral (cM1) and ipsilateral M1 (iM1). Here the iM1 activity is decreased or reduced and cM1 is increased. (B) The healthy subgroup of seven age and gender matched participants reflects a similar asymmetric response pattern (four bars on the left). In comparison, the group of five agenesis patients shows a more symmetric activity pattern, in which particularly the iM1 activity is significantly elevated (four bars on the right; see Section 3). Error bars represent the standard error.

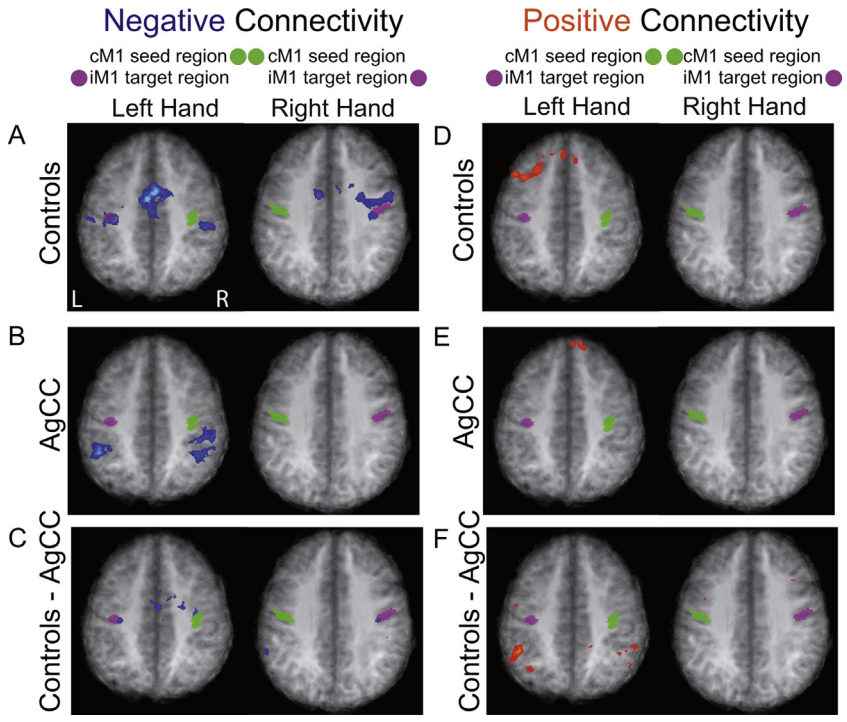

Fig. 3. Functional connectivity maps during unilateral hand movement as estimated by the means of psychophysiological interactions (PPI). As seed region we used the voxels of the contralateral M1 hand activity (green) and estimated which of the voxels in the brain showed a negative (left panel) or a positive (right panel) coupling to this seed region. (A) In the subgroup of seven-matched healthy participant we found strong suppression of voxels (activation map in blue; $p < .05$, FWE corrected) covering voxels near M1 of the other hemisphere (purple). (B) This interhemispheric contralateral to ipsilateral M1 (cM1-to-iM1) suppression was absent in agenesis patients ($p < .05$, FWE corrected). (C) A group comparison demonstrates a stronger interhemispheric cM1-to-iM1 suppression in healthy participants than in agenesis patients ($p < .05$, uncorrected). (D–F) For healthy participants as well as for agenesis patients an interhemispheric cM1-to-iM1 facilitation during unilateral hand movements was absent (activation map in orange; $p < .05$, FWE corrected). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

suppression for AgCC patients. To examine whether the interhemispheric motor suppression is directly modulated by the callosal fibers, we correlated the individual cM1-to-iM1 interhemispheric motor suppression z-value with the individual FA values for the different callosal segments. In a combined multiple-regression analysis with callosal segment FAs as independent variables and cM1-to-iM1 interhemispheric motor suppression as dependent variable, FA of the posterior midbody and the isthmus segments were the only variables providing unique contribution to cM1-to-iM1 interhemispheric motor suppression (posterior midbody segment: $\beta = -.66$, $t(39) = -3.21$, $p = 0.003$; isthmus segment: $\beta = .79$, $t(39) = 3.57$, $p = 0.001$; other predictors: $p > 0.22$). However, separate bivariate correlation analyses for the callosal segments showed that only FA of the isthmus segment correlated with cM1-to-iM1 interhemispheric motor suppression (isthmus segment: $r(43) = .38$, $p = 0.01$, see Fig. 4b). No significant correlations were found between cM1-to-iM1 interhemispheric motor suppression and FA of the other CC segments (posterior midbody segment: $r(43) = .02$, $p = 0.26$; splenium segment: $r(43) = .18$, $p = 0.26$; anterior midbody segment: $r(43) = .28$, $p = 0.06$; anterior third segment:

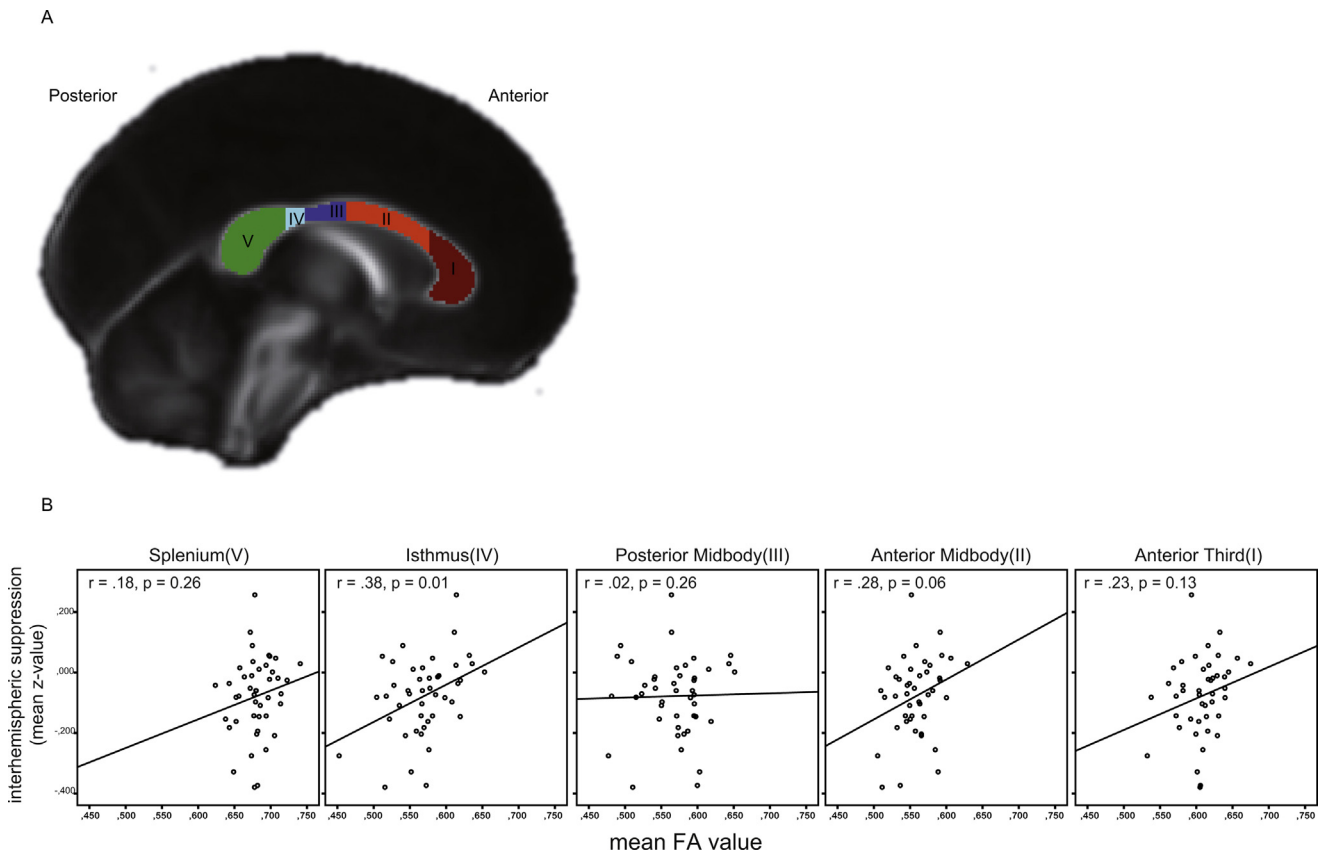

Fig. 4. Schematic description of the geometry-based tract segmentation in the corpus callosum and correlations between transcallosal fibers and interhemispheric BOLD suppression for forty-five healthy participants. (A) Geometry-based tract segmentation in the corpus callosum overlaid onto the FMRIB58 fractional anisotropy template. As defined by the scheme of Hofer and Frahm [30], the whole CC was divided manually into five sub-segments from anterior to posterior along the *y*-axis: anterior third (red), anterior midbody (orange), posterior midbody (blue), isthmus (light-blue) and the splenium (green). (B) Only the fractional anisotropy (FA) of fibers projecting through the isthmus significantly predicted the variability of interhemispheric cM1-to-iM1 suppression. No relations were found between interhemispheric cM1-to-iM1 suppression and FA values of fibers in other callosal sub-segments. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

$r(43) = .23$, $p = 0.13$, see Fig. 4b). A situation in which an independent variable shows no bivariate correlation with the dependent variable, but makes a significant contribution in the context of a multiple-regression analysis with other variables, is called "suppression" in statistics. The variable suppresses noise variance in other independent variables and thereby enhances predictive power of the variable set as a whole [31]. In our data set, the posterior midbody FA seems to act as a suppressor variable, since it is not related to cM1-to-iM1 interhemispheric motor suppression on its own. Therefore, only FA of the isthmus segment is directly associated with the cM1-to-iM1 interhemispheric motor suppression.

4. Discussion

In our study, healthy individuals showed an expected increased BOLD activity of the contralateral M1 and a decreased or reduced ipsilateral M1 activity during unilateral hand movements. Additional functional connectivity analysis revealed negative interhemispheric coupling between contralateral und ipsilateral M1 activities, indicating that ipsilateral activity was primarily suppressed by activity of the contralateral M1. Furthermore, we found that differences in the microstructural properties of callosal fibers interconnecting both M1 correlated with variations of contralaterally induced ipsilateral (cM1-to-iM1) suppression in healthy individuals. In contrast, cM1-to-iM1 suppression was absent in acallosal patients (AgCC), reflecting hemispheric independence for motor functions.

The expected increase in cM1 BOLD activity for unilateral hand movements relative to baseline is in accordance with previous findings [9–11,32]. Increased or positive BOLD activity is associated with the cerebral blood flow and therefore with the metabolism of the underlying structure [33,34] and the neural activity measured by local field potentials [35,36]. For the motor cortex it was shown that increased BOLD responses in M1 were predominantly related to excitatory synaptic activity [37]. Our results reconfirm the prominent role of the cM1 in controlling unilateral hand movements.

However, there is also an involvement of iM1 in motor control in healthy individuals. Early TMS/MEP studies indicate that iM1 can control the ipsilateral hand, most likely through uncrossed corticospinal projections [3–5]. This ipsilateral control is normally inhibited through trancallosal inhibition [4,6] by the cM1 in conditions where crosstalk should be avoided [7,8]. As the temporal resolution of fMRI is relatively poor, BOLD responses of iM1 only represent the net effect of transcallosal inhibition and activation by ipsilateral hand movements [9–11]. Our results indicate a slightly higher activation of iM1 of the non-dominant than of the dominant hand. This significant asymmetric pattern of iM1 activation is in accordance with Hayashi et al. [10] and is potentially induced by asymmetric iM1 involvement in hand control and asymmetric cM1–iM1 interhemispheric inhibition [38]. These two factors also play an important role in the generation of hemispheric dominance in motor control [8]. In addition to studies using TMS and fMRI to detect asymmetric interhemispheric effects in the motor domain,

earlier studies using motor training in humans detected similar differential effects from training in one hand to performance of the other untrained hand. In some studies it is argued that the dominant hemisphere is the only proficient system for motor engrams. This assumption leads to an effect in which the dominant hand benefits more from non-dominant hand training than the other way around, since for the latter, additional interhemispheric transfer of training information is needed when performing the movement afterwards with the untrained non-dominant hand [39,40]. In other studies it is assumed that the dominant hemisphere is the more proficient system for motor engrams, than the non-dominant hemisphere. Here training information is already communicated to the untrained hemisphere during learning. Since the dominant hemisphere stored superior movement standards and the non-dominant hemisphere inferior movement standards, the non-dominant hand benefits more from dominant hand training than the other way around [41–43]. Another reason why the dominant hand does not benefit from the non-dominant hand training is the fact, that the non-dominant hemisphere probably transfers inferior movement standards to the dominant hemisphere, which in turn interfere with existing superior movement standards, leading to a more negative "inhibitory" transfer effect [41]. One possibility to avoid this unwanted crosstalk from the non-dominant hemisphere is a strong interhemispheric inhibition from the dominant to the non-dominant hemisphere. Our data supports this assumption in showing a stronger decreased activation for iM1, by movements of the dominant than non-dominant hand.

By using a functional connectivity approach we were able to show that the iM1 activity was strongly related to the interhemispheric suppression by the cM1. When cM1 was used as seed region for whole brain functional connectivity analyses, mainly voxels in iM1 and in the SMA's of both hemispheres were suppressed. These results suggest that there is a direct cM1-to-iM1 and an additional indirect motor suppression via the SMAs. This is in accordance with findings by Grefkes et al. [44] applying the dynamic causal modeling approach (DCM) for unilateral hand movements. They found a strong negative effective connectivity by the cM1 and the contralateral SMA to the iM1 when participants conducted unilateral hand movements. Interestingly, when participants had to move both hands at the same time, both M1s showed strong positive and reciprocal effective connectivity. Thus, both M1s are able to dynamically switch their interhemispheric interactions from inhibition to facilitation as measured with the BOLD signal. Since our study only includes unimanual hand movements, the facilitatory cM1-to-iM1 interaction is absent in our connectivity analyses.

By using a novel approach we were able to show that interhemispheric cM1-to-iM1 BOLD suppression was related to the microstructural properties of the isthmus, which is likely to be the projecting zone of callosal motor fibers in humans [45]. Physiological interpretation of diffusion properties are challenging because diffusion anisotropy can be influenced by a number of factors, including myelination, fiber density or axon diameter [46]. Increased myelin thickness and high fiber density hinders radial diffusion of water molecules and are therefore related to high FA values in a given voxel. Light microscopic analysis of the human callosal fiber composition revealed clear regional differences [1]. For the posterior midbody and the isthmus it was shown that these regions consist of larger-diameter, myelinated and less densely packed fibers. The myelin or fiber density hypothesis would predict that individuals with increased myelin thickness and/or more densely packed callosal motor fibers, would show stronger interhemispheric motor suppression. Our data supports this hypothesis in showing a positive correlation between FA values in the isthmus and *z* values representing the cM1-to-iM1 BOLD suppression. This is in accordance with previous studies investigating the link between TMS induced interhemispheric motor inhibition and callosal microstructure [13,14]. They found the same relationship that the stronger the interhemispheric inhibition the higher the FA values in specific callosal regions covering mostly the posterior midbody and parts of the isthmus. Another recent study showed that also macroscopic properties (callosal thickness) of the isthmus is associated to unilateral hand performance where interhemispheric inhibition is important [47]. Further evidence that fibers of the isthmus and posterior third are important for interhemispheric motor suppression comes from TMS studies in AgCC patients. Meyer and colleagues investigated whether patients with complete [20] or partial AgCC [21] show TMS induced ipsilateral silent periods (iSPs). Transcranial magnetic stimulation of M1 in one hemisphere produces motor evoked potentials (MEPs) in contralateral muscles transmitted through corticospinal tracts [3]. For ipsilateral muscles there is an initial short period of an increased MEP signal, induced by uncrossed corticospinal projections [5], followed by a longer period of a MEP signal suppression. The latter period is also known as iSP, which is related to transcallosal motor inhibition induced by the contralateral M1 [3]. In patients with complete agenesis, the iSP is absent [20]. For patients with partial AgCC it was shown that only the group of patients who had lesions covering the isthmus/posterior third of the CC did not show iSPs [21], indicating that only fibers projecting to this region are essential for interhemispheric motor suppression.

We think that the abnormal increase in iM1 activity in AgCC has at least two causes: (i) an enhanced ipsilateral motor projection [5] and/or (ii) a lack of interhemispheric cM1-to-iM1 suppression due to the absence of callosal fibers. Previous research indicates that the contribution of ipsilateral motor projections to hand movements are negligible [48]. Therefore, we assume that the latter factor is important in explaining our findings.

In healthy participants, we found that cM1-to-iM1 suppression is mediated by specific callosal fibers, whereas in AgCC patients this suppression is absent. This suggests that the absence of callosal motor fibers had a major impact on the cM1-to-iM1 disinhibition and thus the elevated iM1 activity. In a previous study Reddyet al. [49] showed that acallosal patients demonstrate a similar BOLD activity of iM1 like controls, which is contrast to our findings. One reason for this discrepancy could by that Reddy et al. [49] used a voxel count procedure to detect iM1 BOLD activity. Our approach focused more on the amplitude of the BOLD response in iM1 and the interhemispheric functional negative connectivity in iM1 induced by cM1. We used these procedures, since several other researchers show that this kind of analyses is more suited to detect this type of neural phenomenon [9,10,44]. Therefore we think that our findings and results from previous TMS studies in AgCC patients [20,21] clearly demonstrate that interhemispheric motor suppression in these patients is massively affected. Interestingly, this reduction of cM1-to-iM1 inhibition is also apparent when the corpus callosum is intact but functions of motor areas are affected after stroke. Using TMS Murase et al. [50] show that interhemispheric cM1-to-iM1 suppression is important for accurate motor control, since it is very strong immediately preceding the unilateral hand movement in healthy individuals. In stroke patients, this suppression is absent when they move their affected hand. Similarly to our findings in the acallosal subjects, the study in stroke patients also showed that the reduction of cM1-to-iM1 inhibition also lead to an increased iM1 BOLD activity when the affected hand was moved [51].

The findings and proposed model by [10] and results of our data indicate that callosal suppression shapes the asymmetric BOLD responses in cM1 (high) and iM1 (low or negative) during unilateral hand movements. Research indicates that callosal suppression is also important in the establishment of brain asymmetries and handedness [8,52,53]. It has been proposed that distal hand movements are initially generated bilaterally, and only during the final preparation phase the movement becomes uni-

lateral through transcallosal inhibition [50,54]. The healthy and adult human population consists of 90% right-handed and 10% left-handed or ambidextrous individuals [55,56]. In adults with complete AgCC, this distribution is different in that only 70% are right-handed and 30% are left-handed or ambidextrous [57–60]. One significant factor for this shift in handedness distribution in AgCC patients could be the absence of transcallosal suppression during the final preparation phase of hand control. This in turn could trigger bilateral involvement during the final preparation phase, which would weaken the strong motor dominance of one hemisphere. Further support for this hypothesis is the finding that infants show a less pronounced lateralization of handedness compared to healthy adults. It was shown that only 70% of the infants were right-handed and the remaining 30% were left-handed or ambidextrous [61]. This finding could be explained by the fact that there is a continued development of the corpus callosum throughout childhood and adolescence [62,63]. The late maturation of the transcallosal inhibitory system [64,65] could be one aspect in boosting (from 70% to 90%) and sustaining the motor dominance of one hemisphere at a later age. Interestingly, Sacco et al. [61] also investigated in the same study the handedness in infants with complete AgCC. Similar to the healthy infants and to the adult complete AgCC patients their handedness distribution was 65% right-handed and 35% left-handed or ambidextrous. The unchanged pattern of handedness distribution in older AgCC could potentially be caused by the absence of callosal maturation.

5. Conclusions

In conclusion, we have shown that interhemispheric inhibition during intended unilateral hand movements is related to properties of specific fibers in the corpus callosum of healthy humans. In addition, we found that the inhibitory interaction between motor areas is diminished when the corpus callosum is absent. This provides further evidence in humans for the inhibitory function of the corpus callosum in the motor system and may provide novel aspects into the neurobiological underpinnings of communication of two hemispheres and establishment of brain asymmetries in general.

Conflict of interest

The authors declare no conflict of interest.

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