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Interlimb transfer of reach adaptation does not require an intact corpus callosum: Evidence from patients with callosal lesions and agenesis
Interlimb transfer of reach adaptation does not require an intact corpus callosum: Evidence from patients with callosal lesions and agenesis.

Abbreviated Title: Interlimb transfer despite callosal abnormalities

Penelope A. Tilsley¹, Patricia Romaiguère¹, Eve Tramoni²,³, Olivier Felician²,³ & Fabrice R. Sarlegna¹*

¹ Aix Marseille Univ, CNRS, ISM, Marseille, France
² Aix Marseille Univ, INSERM, INS, Inst Neurosci Syst, Marseille, France
³ APHM, CHU de la Timone, Service de Neurologie et Neuropsychologie, Marseille, France

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*Correspondence should be addressed to: Fabrice Sarlegna, Institute of Movement Sciences, 163 av. de Luminy – CP 910, 13009 Marseille, France.
E-mail: fabrice.sarlegna@univ-amu.fr

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Conflict of interest

Authors report no conflict of interest.

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Abstract

Generalization of sensorimotor adaptation across limbs, known as interlimb transfer, is a well-demonstrated phenomenon in humans, yet the underlying neural mechanisms remain unclear. Theoretical models suggest that interlimb transfer is mediated by interhemispheric transfer of information via the corpus callosum. We thus hypothesized that lesions of the corpus callosum, especially to its midbody connecting motor, supplementary motor and premotor areas of the two cerebral hemispheres, would impair interlimb transfer of sensorimotor adaptation. To test this hypothesis, we recruited three patients: two rare stroke patients with recent, extensive callosal lesions including the midbody and one patient with complete agenesis. A prismatic adaptation paradigm involving unconstrained arm reaching movements was designed to assess interlimb transfer from the prism-exposed dominant arm to the unexposed non-dominant arm for each participant. Baseline results showed that spatial performance of each patient did not significantly differ from controls, for both limbs. Further, each patient adapted to the prismatic perturbation, with no significant difference in error reduction compared to controls. Crucially, interlimb transfer was found in each patient. The absolute magnitude of each patient’s transfer did not significantly differ from controls. These findings show that sensorimotor adaptation can transfer across limbs despite extensive lesions or complete absence of the corpus callosum. Therefore, callosal pathways connecting homologous motor, premotor and supplementary motor areas are not necessary for interlimb transfer of prismatic reach adaptation. Such interlimb transfer could be mediated by transcallosal splenium pathways connecting parietal, temporal and visual areas, ipsilateral cortico-spinal pathways or subcortical structures such as the cerebellum.
Significance Statement

Theoretical models suggest that interlimb transfer of sensorimotor adaptation is mediated by interhemispheric interactions via the corpus callosum, specifically between motor cortices. We thus hypothesized that interlimb transfer of prism adaptation in a reaching task would be impaired in patients with callosal abnormalities, especially those affecting midbody pathways connecting the motor cortices. Contrarily, we found interlimb transfer in each patient, to a level comparable to that of controls. Our findings show that callosal pathways connecting motor, premotor and supplementary motor areas are not necessary for the interlimb transfer of prismatic reach adaptation. Alternatively, this transfer could be mediated by ipsilateral cortico-spinal pathways, subcortical structures such as the cerebellum or callosal splenium pathways connecting parietal, temporal and visual areas.
Introduction

When we are exposed to novel properties of the body or the environment, motor behaviour is optimized through trial-by-trial fine-tuning of sensorimotor neural networks, an adaptation thought to evolve through the iterative comparison of the planned and executed movements (Luauté et al., 2009; Shadmehr et al., 2010; Wolpert et al., 2011). One feature of this sensorimotor adaptation is that it is not necessarily specific to the conditions in which it was acquired, but can generalize to a different task (Morton and Bastian, 2004) or a different effector (Green and Gabriel, 2018; Lee et al., 2010; Stöckel et al., 2016; Taylor et al., 2011; Wang and Sainburg, 2003). Transfer between effectors, termed interlimb transfer, has been repeatedly evidenced in studies of upper-limb movements aiming to determine the local or global nature of the adaptive process (Criscimagna-Hemminger et al., 2003; Dizio and Lackner, 1995; Harris, 1965; Joiner et al., 2013; Malfait and Ostry, 2004; Renault et al., 2020), yet the underlying neural mechanisms remain unclear (Ruddy and Carson, 2013).

Longstanding theoretical models of the neural mechanisms of interlimb transfer highlight the key role of the corpus callosum, the largest white matter tract connecting the two cerebral hemispheres (Parlow and Kinsbourne, 1990, 1989; Taylor and Heilman, 1980). The Callosal Access Model (Taylor and Heilman, 1980) proposes that unimanual adaptation is encoded within the contralateral hemisphere and is accessible, via the corpus callosum, to the opposite hemisphere-arm system (see also Sainburg and Wang, 2002). The Cross-Activation Model (Parlow and Kinsbourne, 1990, 1989) proposes that unimanual adaptation is encoded in the contralateral hemisphere, and copied, via the corpus callosum, to the opposite hemisphere-arm system. Lee et al. (2010) later provided neurophysiological evidence that both the contralateral and ipsilateral motor cortices are involved in both adaptation and interlimb transfer of adaptation.
Perez et al. (2007a) also provided evidence that interlimb transfer of sequence learning is driven by bilateral supplementary motor areas, connected via the corpus callosum midbody (Fabri et al., 2014; Ruddy et al., 2017). Further, Perez et al. (2007b) reported that interlimb transfer was related to modulations of the transcallosal midbody pathways connecting homologous motor cortices (see also Ruddy and Carson, 2013). These studies thus suggest that the corpus callosum, and in particular its midbody segment that connects motor, supplementary motor and premotor regions bilaterally, plays a key role in interlimb transfer.

One approach which has led to key insights into the functional role of callosal pathways has been to study neurological individuals with corpus callosum abnormalities (Volz and Gazzaniga, 2017). Using this approach, interlimb transfer was shown to be impaired in agenesis patients and split-brain patients (de Guise et al., 1999), and multiple sclerosis patients with corpus callosum atrophy (Bonzano et al., 2011). The results of these studies are in line with the aforementioned theoretical models (Parlow and Kinsbourne, 1990, 1989; Taylor and Heilman, 1980). However, Thut et al. (1997) found interlimb transfer of proximal drawing movements in agenesis patients and a traumatic brain injury patient with corpus callosum damage. Criscimagna-Hemminger et al. (2003) also reported interlimb transfer of force-field reach adaptation in a split-brain patient, whose corpus callosum was surgically sectioned to alleviate severe epilepsy. These two studies thus cast doubt on the generalizability of the dominant theories of interlimb transfer.

The present study aimed to determine the role of the corpus callosum in the interlimb transfer of sensorimotor adaptation by assessing transfer in one patient with complete agenesis as well as two stroke patients with callosal damage. The two stroke patients presented a rare opportunity to assess the impact of recent, non-surgical callosal lesions in typically developed adults with no epilepsy. Patients and matched controls were tested on a prism adaptation paradigm involving
unconstrained arm reaching movements. This paradigm, used in both fundamental and rehabilitation contexts (Harris, 1963; Martin et al., 1996a; Rossetti et al., 1998), is known to result in after-effects on the exposed arm but also on the non-exposed arm, evidencing interlimb transfer (Hamilton, 1964; Renault et al., 2020). The methodological procedure employed here was based on previous work (Dizio and Lackner, 1995; Harris, 1963; Kitazawa et al., 1997; Lefumat et al., 2015; Martin et al., 1996a) and allowed assessment of transfer for each individual (Renault et al., 2020), a critical issue when studying unique patients (Lefumat et al., 2016).

Based on previous research highlighting the role of the corpus callosum in interlimb transfer, we hypothesized that patients lacking callosal connections between motor, premotor and supplementary motor areas would show impaired interlimb transfer of sensorimotor adaptation.
Materials and Methods

Participants

Three patients with corpus callosum disorders (MS, MM and AM) and 16 healthy individuals participated in the study. The number of healthy participants reflect the sample size used in similar studies (Bao et al., 2020; Fleury et al., 2020; Leclere et al., 2019; Lefumat et al., 2015; Morton and Bastian, 2004; O’Shea et al., 2014; Perez et al., 2007a; Renault et al., 2020; Striemer et al., 2019; Wang and Sainburg, 2003). Patient MS was a 51-year-old left-handed female with recently acquired lesions of the body of the corpus callosum, sparing the splenium and the genu. Patient MM was a 29-year-old right-handed male also with recently acquired lesions of the corpus callosum, sparing only the splenium. Patient AM was a 50-year-old right-handed male with complete agenesis of the corpus callosum (see Table 1 and full patient descriptions below). All patients and controls had normal or corrected-to-normal vision, with control participants declaring no previous or current sensorimotor or neurological deficits. Handedness was determined using the 10-item version of the Edinburgh Handedness Inventory (Oldfield, 1971).

Considering the patients’ characteristics, two control groups were recruited: Group A: age = 52 ± 4 years, n = 8 (5 right-handed males; 3 left-handed females) and Group B: age = 29 ± 4 years, n = 8 (8 right-handed males). As developed later, the differences between the patients led us to compare each patient (instead of the group of patients) to control participants.

Before taking part in the experiment, participants were presented with an information sheet on the protocol, filled out the Edinburgh Handedness Inventory, and gave their written informed consent to participate. Participants could leave the experiment at any time and were free to ask questions to the experimenter; they were kept as naïve as possible to the exact purpose of the
study. The study was approved by the local institutional review board and performed in accordance with the standards laid out by the Declaration of Helsinki (1964).

Patients’ profiles

Patient MS was a left-handed female (Laterality Quotient: -100%), 51-years-old at the time of testing (March 2017). MS had suffered from a ruptured brain aneurysm in the anterior cerebral artery 2.5 years previously at 48-years old (August 2014). This resulted in damage to the whole body of the corpus callosum, with only the anterior (genu) and posterior (splenium) regions being preserved (Figure 1B), as well as hemosiderin deposits in the left and right cingulum. Patient MS thus presented a rare haemorrhagic stroke subtype (Li et al., 2015), which allowed us to study the impact of an insult to the corpus callosum in an individual with a normal development and no known neurological disorder (e.g. no epilepsy) prior to the corpus callosum damage. With regards to motor function, clinical tests (see Table 1) indicated slight ideomotor apraxia in performing gestures with the left hand and impaired somatosensory transfer between the two arms. In the months following the acute haemorrhage, she also reported recurrent conflicts between the two hands as depicted in the setting of corpus callosum injury under the terms of diagnostico dyspraxia (Akelaitis, 1945) or alien hand syndrome (Biran et al., 2006). For instance, patient MS stated that when trying to open the wardrobe with one hand to select an item of clothing, the other hand would shut it. When tested for this experiment, the patient reported that intermanual conflicts had mostly resolved, with very occasional symptoms reappearing with stress or fatigue. Neuropsychological assessments undertaken between 2015 and 2017 indicated...
a normal global cognitive functioning with below average attentional capacity and short-term memory.

Patient MM was a right-handed male (Laterality Quotient: 75%), 29-years-old at the time of testing (January 2019). MM had an ischemic stroke in the territory of the bilateral anterior cerebral arteries following an intravascular thrombus in August 2018. This resulted in extensive lesions to the anterior and mid cingulate gyrus, and the rostrum, genu and body of the corpus callosum, sparing only the posterior (splenium) region (Figure 1C). Clinical testing (see Table 1) showed that the patient displayed moderate motor slowing with a mild motor apraxia predominantly on the left side and occasional troubles in movement initiation. The patient also reported intermanual conflicts, with the left hand interfering with the actions performed by the right hand. For example, when opening a door with the right hand, the left hand would try to shut it. Neuropsychological assessments also revealed sustained attention and memory deficits. Patient MM thus provided another rare opportunity to study the effect of a recent lesion involving the corpus callosum in an adult with typical development.

Patient AM was a right-handed male (Laterality Quotient: 80%), 50-years-old at the time of testing (February 2018). AM had complete congenital agenesis of the corpus callosum (Figure 1D) and posterior commissure, left hippocampal sclerosis, and a history of complex partial seizures in the setting of mesial temporal lobe epilepsy. Full patient details can be found in Ridley et al. (2016), but in summary, AM endured status epilepticus in March 2012. One month later, despite full resolution of epileptic seizures, AM developed intermanual conflicts: for instance, when putting on a pair of trousers with the left hand, the right hand would pull them off (Ridley et al., 2016). Neuropsychological assessment revealed right-sided constructional apraxia, right ideomotor apraxia and right visual anomia, showing signs of inter-hemispheric
disconnection. Global cognitive functioning was low to average. Follow-up assessments carried out in the following years indicated significant amelioration of diagonistic dyspraxia and inter-hemispheric disconnection features (see Table 1). Testing patient AM allowed us to explore the influence of complete absence of the corpus callosum throughout development.

Experimental setup

Participants were seated in front of a horizontal table positioned at waist height. The table was equipped with a raised, red start button (2cm in diameter) located at 0° (straight-ahead) according to the body midline, directly in front of the participants chest. The start button was present at all times during the experiment. Given that the lights of the experimental room were on throughout the experiment, participants could thus both see and feel for the start button position. Red light-emitting diodes (3mm in diameter) on the table were used as visual targets (Figure 2). Three targets were used in this study, all located 37cm from the starting position: a middle target located at 0° (straight-ahead), a rightward target located at +20° and a leftward target located at -20° with respect to the body midline. Participants were required to wear either standard (control) goggles or altered (17° rightward deviating prismatic) goggles equipped with 30-diopter Fresnel 3M Press-on plastic lenses (3M Health Care, St Paul, Minn., USA), as used in Martin et al. (1996b). Welding goggles were used so that vision was only possible through the lenses (O’Shea et al., 2014). The use of a head restraint was avoided based on results of Hamilton (1964) showing that restraining the head precludes interlimb transfer of prism adaptation.
Infrared active markers were taped to the right and left index fingertips and their positions were sampled at 350Hz using an optical motion tracking system (Codamotion cx1 and MiniHub, Charnwood Dynamics Ltd, Leicestershire, UK). The experimenter controlled the motion tracking system as well as the protocol using a customized software and a real-time acquisition system (ADwin-Pro, Jäger, Lorsch, Germany). An infra-red camera allowed continuous real-time monitoring by the experimenter of the participants’ behaviour and progression of the experiment. A standard video-camera was also placed, just above the height of the table in front of the participant, for replay in case of technical, kinematic or other issues. Data loss from the Codamotion motion tracking system on a crucial after-effect trial for one of the patients led to analysis performed on the video-camera recording (detailed in the legend of corresponding figures).

**Experimental procedure**

The experiment consisted of a series of arm reaching movements, performed with either the dominant or the non-dominant arm, from the starting position toward a visual target. The visual target was flashed 1s after the beginning of a trial for a short duration of 0.3s, so that by the time participants had reached the target, it had disappeared. Two auditory tones were then used to inform participants of key timepoints of the trial: a 100ms-long beep occurring 1.6s after trial onset to inform participants they could return slowly to the starting location and a 600ms-long beep occurring 7.4s after trial onset to inform the participant that the trial had ended. This timing was chosen to allow a slow return movement back to the start button in order to reduce the impact of the return phase on the adaptation process, as Kitazawa et al. (1997) showed velocity-
specific prismatic adaptation and the return phase was not analysed within the results. Each trial was 8s long in total and the next trial started automatically once the previous trial had ended.

Participants were instructed to reach as fast and as accurately as possible toward the visual target in a natural, unconstrained movement. Participants were asked to lift their finger off the table, rather than slide directly across the table and not correct the end position of their finger once it had hit the table. On the return movement, participants were asked to go back slowly to the starting position to minimize the effect of this return phase on the adaptation process. Participants were allowed to return to the start position by sliding their finger along the table. In order to achieve consistent task completion and reduce learning effects during baseline, participants were familiarized with the task by performing 30 reaching movements with both arms under normal visual conditions without prisms before starting the experimental phases. Lastly, participants were instructed not to move their opposite arm during and between trials being performed with the designated arm.

To assess sensorimotor adaptation and interlimb transfer, we employed a procedure inspired by previous work (Dizio and Lackner, 1995; Harris, 1963; Kitazawa et al., 1997; Lefumat et al., 2015; Martin et al., 1996a) and recently used by Renault et al. (2020). The experimental session consisted of 3 phases (presented in Figure 2): a baseline pre-exposure phase under normal vision (baseline phase), a prism exposure phase with prismatic perturbation (prism phase) and a post-exposure phase under normal vision (post phase). During the baseline phase, participants performed 30 reaching movements with the dominant arm, then 30 movements with the non-dominant arm toward one of the three targets while wearing standard control goggles. The targets were presented in a randomised order which was the same for each participant with, ultimately, 10 trials per target for each arm. The order of experimental conditions in the baseline
phase was not counterbalanced, as in other studies (Lefumat et al., 2015; Renault et al., 2020; Wang et al., 2011), because it was desired that all controls and patients performed exactly the same protocol to strengthen control-patient comparisons. When the baseline phase was over, participants had a 2-minute break during which they were asked to stay motionless with the eyes closed while the control goggles were replaced with prismatic goggles.

During the following prism phase, participants performed 100 movements (Control Group A, patient MS and patient AM) or 50 movements (Control Group B and patient MM) toward the middle 0° target with the dominant arm while wearing the 17° rightward deviating prismatic goggles. Patient MM, and subsequently Control Group B, completed 50 of the desired 100 movements due to patient MM experiencing tiredness of the right shoulder during this prism phase. The group factor was thus included in the statistical design. At the end of this phase, another 2-minute break was given during which participants were instructed to keep their eyes closed and remain motionless, while the prismatic goggles were replaced with the control goggles.

During the post phase, participants first performed 30 reaching movements with the unexposed non-dominant arm, before performing 30 movements with the dominant arm again resulting in 10 trials per target per arm under normal vision. During this post phase, the first target presented (post 1 trial) was always the middle straight-ahead 0° target, before all remaining targets were presented in a randomised fashion. The order of experimental phases was selected, as in previous studies (Lefumat et al., 2015; Renault et al., 2020), to have the non-dominant arm baseline and post-phases immediately before and after the dominant arm prism adaptation phase. Any difference in non-dominant arm performance could thus be directly attributed to dominant arm prism adaptation, thus showing interlimb transfer.
Interlimb transfer of sensorimotor adaptation was investigated from dominant arm to non-dominant arm based on experimental studies showing unidirectional transfer from the dominant arm to the non-dominant arm (Balitsky Thompson and Henriques, 2010; Galea et al., 2007; Mostafa et al., 2014) and, in particular, the study by Criscimagna-Hemminger et al. (2003) which also challenged the role of the corpus callosum in the interlimb transfer of sensorimotor adaptation. Adaptation during the prism phase was performed only toward the middle 0° target so that it would be possible to explore, for both arms, the extent of generalization across target directions in the post phase compared to the baseline phase. This was based on previous literature (Lefumat et al., 2015; Renault et al., 2020), which found significant generalization for the exposed arm but not the unexposed arm. However, to keep the main message of the article clear and not unnecessarily lengthen the manuscript, analysis of the movements toward the lateral targets was not included in the manuscript. Interlimb transfer was thus assessed by comparing baseline movements toward the middle target, performed just before prism adaptation, to the first movement of the post phase toward the middle target, performed just after prism adaptation. This movement was thus performed immediately after prism adaptation and was not influenced by movements to the lateral targets. The experiment took approximately one hour.

**Kinematic data analysis**

Data were analysed using Matlab (Mathworks, Natick, MA, USA) and Microsoft Excel 2017. A few trials (1.8%) had to be discarded due to either the participant not making a movement toward the target, the participant moving before the target had appeared, or technical problems. Position
data from the markers on the right and left index fingertips were low-pass filtered with a dual-pass, no-lag Butterworth filter (cut-off frequency: 8Hz; order: 2). Movement onset and offset were defined as the first time at which hand velocity went above 3cm/s or dropped below 3cm/s respectively (as in Lefumat et al., 2015; Renault et al., 2020). Kinematic variables calculated and reported included: initial movement direction, final movement direction, end point accuracy, maximum perpendicular deviation, peak velocity, time to peak velocity, movement time and reaction time. Initial movement direction was computed as the angle between the vector from the start position to the target position and the vector from the start position to the hand position at peak velocity (Wang and Sainburg, 2003; Renault et al., 2020). Final movement direction was calculated as the angle between the vector from the start position to the target position and the vector from the start position to the hand position at movement offset. End point accuracy was computed as the Euclidian distance in cm between the hand end position and the target position. Maximum perpendicular deviation was calculated as the maximum horizontal (x axis) distance in cm between the movement trajectory path and the theoretical straight line connecting the start position and the target position (Malfait and Ostry, 2004; Shadmehr and Moussavi, 2000).

The kinematic variable of interest for examining the prismatic effects throughout the experiment was the initial movement direction as this mostly reflects the initial motor plan before visual feedback loops influence the movement (O’Shea et al., 2014; Reichenbach et al., 2014; Sarlegna and Mutha, 2015). Maximum perpendicular deviation was also reported to verify prismatic adaptation and transfer effects, noted as giving similar results by Malfait and Ostry (2004).
R3.6.0 (R Core Team, 2018), Statistica 8 (StatSoft, Tulsa, OK, USA) and Excel 2017 were used to perform statistical analysis. Statistica was used to assess normal distribution with the Kolmogorov-Smirnov method, perform t-tests and ANOVAs, and carry out Tukey post-hoc analysis of control data. Excel 2017 was used to calculate individual 98% confidence interval boundaries for both controls and patients, using individual participant’s own baseline data. Confidence intervals were constructed for the normally distributed data using confidence interval formula including the mean ($\bar{x}$), two-tailed t value (t) standard deviation (s) and sample size (n).

A two-tailed design at 98% confidence was used in order to test for deviation in either direction with an $\alpha/2$ of 0.01 ($p < 0.02$) and t values were used due to a small sample size of baseline trials ($n < 30$) (Moore et al., 2009; Pek et al., 2017), with 10 trials per target per arm. R using parts of the psycho (v0.5.0; Makowski, 2018) package, was used to perform Crawford’s modified t-test. This method, adapting an independent sample pooled t-test for use with a sample of $n = 1$ (one patient), was used to compare each patient’s performance to that of a control sample (Crawford and Garthwaite, 2007). Results were compared with a Bayesian method using the software Single_Bayes_ES, with similar results obtained (Crawford et al., 2010). Z values were reported as an indicator of effect size. The Kolmogorov-Smirnov method showed all data to be normally distributed.

Analysis of control group baseline kinematics consisted of 2x2 ANOVAs including the 2 Groups: Group A and Group B and 2 Arms (repeated measures): dominant arm and non-dominant arm. The factor group (2 Groups: Group A: age = 52 ± 4 years, 100 trials, $n = 8$ and Group B: age = 29 ± 4 years, 50 trials, $n = 8$) was included within all analyses to check for putative effects. Kinematic variables assessed included: initial movement direction, final
movement direction, end point accuracy, maximum perpendicular deviation, peak velocity, time
to peak velocity, movement time and reaction time. Patient values were then compared to the
control group for each patient, across each arm individually, using Crawford’s modified t-test.

Analysis of controls’ dominant arm adaptation consisted of a 2x16 ANOVA on initial movement
direction including the 2 groups: Group A and Group B, and 16 dominant arm phases (repeated
measures): baseline 10 trial average, prism trials 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, prism 11-20 10 trial
average, prism 21-30 average, prism 31-40 average and the prism 41-50 last common average, as
well as the post 1 trial. On an individual level, including both controls and patients, prismatic
effects and after-effects according to initial movement direction and maximum perpendicular
deviation were explored by comparing specific trials (prism phase trials and the post 1 trial
respectively) to the individual’s baseline 98% confidence intervals. Trials falling above or below
the baseline 98% confidence interval boundaries were deemed to be significantly different to
baseline. The number of trials for each participant to reduce errors caused by the prismatic
perturbation (error-reduction rate) was taken as the first prism phase trial to return within the
98% baseline confidence intervals. The prismatic-effect and after-effect for the dominant arm of
each individual were then quantified by calculating the difference between the baseline phase
average and the prism 1 and post 1 values respectively. Patient prismatic-effects, error-reduction
rates and after-effects were then compared to the control group average using Crawford’s
modified t-test.

Analysis of control group non-dominant arm data exploring interlimb transfer effects consisted
of a 2x2 ANOVA on initial movement direction data including the 2 groups: Group A and Group
B and the 2 phases (repeated measures): baseline 10 trial average and post 1. For each individual,
the non-dominant arm post 1 trial was compared to the baseline 98% confidence intervals to
determine the presence of interlimb transfer according to both initial movement direction and maximum perpendicular deviation. A post 1 trial falling above or below the baseline 98% confidence interval boundary was deemed to be significantly different compared to baseline and thus showing interlimb transfer. The interlimb transfer value was then quantified for each individual as the difference between the baseline value and the post 1 value and transformed into an absolute value to compare the amplitude of transfer without directional effects. Patients’ transfer-effects were then compared to the control group average using Crawford’s modified t-test. For control group and patient-control comparisons, the significance threshold was set to 0.05.

The ANOVAs performed on controls’ data included 10-trial averages as well as individual trials, in line with previous research (Leclere et al., 2019; Lefumat et al., 2015; Morton and Bastian, 2004; Renault et al., 2020; Taylor et al., 2011). This was because, in the current study, data analyses revealed some blocks of trials with homogenous performance and blocks of trials with variable performance. Averaging trials thus made sense when motor performance was stable and homogenous, as in baseline and late prism trials, to have a better estimate of performance. However, when large variations were observed between consecutive trials, such as during the initial prism error-reduction phase and post phase, individual trials were kept separate to avoid masking an effect such as interlimb transfer (Taylor et al., 2011).
Results

Baseline motor control

Participants were asked to reach as fast and as accurately as possible toward visual targets with either the dominant (DA) or non-dominant (NDA) arm, under normal visual conditions with visual feedback of the arm at all times. Figure 3 shows baseline trajectories toward the straight-ahead target for an example control participant and three neurological patients with corpus callosum abnormalities. Figure 3 shows that controls, patients MS and MM, whose corpus callosum was severed by a stroke, as well as patient AM, who has a complete corpus callosum agenesis, were able to reach to the target. Hand path trajectories for patients and controls seemed comparably straight and accurate, suggesting that the callosal patients had a normal spatial organization of the movements.

Control participants’ baseline data were analysed with a mixed factor 2x2 ANOVA including 2 arms (DA and NDA) and 2 groups (Group A and Group B). Interlimb differences were found on certain control group kinematics (Figure 4) as the ANOVA showed a simple arm effect for final movement direction (controls average ± standard deviation: DA = 1.8 ± 1.4°, NDA = 0.4 ± 1.0°; $F_{1,14} = 17.0; \eta_p^2 = 0.55, p = 0.001$), end point accuracy (DA = 1.5 ± 0.5 cm, NDA = 1.8 ± 0.6 cm; $F_{1,14} = 4.6; \eta_p^2 = 0.25, p = 0.049$), peak velocity (DA = 1.9 ± 0.3 m/s, NDA = 1.7 ± 0.2 m/s; $F_{1,14} = 7.9; \eta_p^2 = 0.36, p = 0.014$), movement time (DA = 486 ± 80 ms, NDA = 510 ± 70 ms; $F_{1,14} = 8.0; \eta_p^2 = 0.37, p = 0.013$) and reaction time (DA = 289 ± 58 ms, NDA = 270 ± 57 ms; $F_{1,14} = 8.5; \eta_p^2 = 0.38, p = 0.011$). There were no significant group effects nor interactions. Patient values were thus compared to the whole control group ($n = 16$).
Each patient’s baseline average was compared to the controls using Crawford’s modified t-test for each kinematic variable and each arm individually. This analysis showed that the motor performance of patient AM significantly differed from controls only on maximum perpendicular deviation with a more leftward deviation than controls for both the DA (controls = 0.5 ± 1.2 cm, AM = -2.7 ± 0.7 cm; \( z = -2.71, p = 0.019 \)) and NDA (controls = 0.9 ± 1.2 cm, AM = -2.9 ± 0.9 cm; \( z = -3.30, p = 0.006 \); Figure 4D). Patient MS showed one significant difference with a longer time to peak velocity than controls, for both the DA (controls = 170 ± 22 ms, MS = 255 ± 34 ms; \( z = 3.90, p = 0.002 \)) and NDA (controls = 171 ± 17 ms, MS = 211 ± 37 ms; \( z = 2.34, p = 0.039 \)); Figure 4F). Patient MM, tested the soonest after corpus callosum insult, showed a reduced peak velocity for both the DA (controls = 1.9 ± 0.3 m/s, MM = 1.1 ± 0.1 m/s; \( z = -2.96, p = 0.011 \)) and NDA (controls = 1.7 ± 0.2 m/s, MM = 1.2 ± 0.2 m/s; \( z = -2.68, p = 0.020 \); Figure 4E), a longer time to peak velocity for both the DA (controls = 170 ± 22 ms, MM = 249 ± 55 ms; \( z = 3.62, p = 0.003 \)) and NDA (controls = 171 ± 17 ms, MM = 255 ± 2 ms; \( z = 4.88, p < 0.001 \); Figure 4F) and a longer movement time for both the DA (controls = 486 ± 80 ms, MM = 686 ± 41 ms; \( z = 2.49, p = 0.028 \)) and NDA (controls = 510 ± 70 ms, MM = 754 ± 56 ms; \( z = 3.48, p = 0.004 \)).

Patient MM also exhibited a longer reaction time for the DA (controls = 289 ± 58 ms, MM = 553 ± 194 ms; \( z = 0.0005, p = 0.018 \)) but not the NDA (controls = 270 ± 57 ms, MM = 379 ± 95 ms; \( z = 1.91, p = 0.083 \); Figure 4H) indicating a larger arm effect than the control group for this variable. Overall, baseline results show that all patients were able to reach accurately toward the visual target when considering initial and final errors: some temporal differences were observed but the spatial organization of the movements was comparable between the patients and controls.
Prismatic adaptation of the dominant arm

To assess sensorimotor adaptation with the DA, participants were asked to perform reaching movements with the DA before (baseline phase), during (prism phase) and after (post phase) prismatic exposure. For controls \( n = 16 \), a 2x16 ANOVA of peak velocity showed no significant group effect \( (F_{1, 14} = 1.78, \eta^2_p = 0.11, p = 0.203) \) or interaction \( (F_{15, 210} = 1.20, \eta^2_p = 0.08, p = 0.275) \) and a significant effect of phase \( (F_{15, 210} = 2.25, \eta^2_p = 0.14, p = 0.006) \). Tukey post-hoc analysis showed that the phase effect was due to an augmented peak velocity on prism 1 (2.0 ± 0.4 m/s) compared to subsequent prism trials 4, 6, 7, 8, 9 and 10, with peak velocities in the range of 1.7-1.8 m/s (p value range < 0.001 to 0.046). No significant differences were observed between baseline peak velocity (1.9 ± 0.3 m/s) and any of the subsequent prism phases (combined peak velocity = 1.8 ± 0.3 m/s, all \( p \) values > 0.49) or the post 1 trial (1.8 ± 0.4 m/s, \( p \) value > 0.99). For patient MS, peak velocity did not significantly differ from controls \( n = 16 \) in any phase. Patient AM showed few significant differences compared to controls with an increased peak velocity on prism 1 (controls = 2.0 ± 0.4 m/s, AM = 3.1 m/s; \( z = 2.40, p = 0.035 \)) and prism 5 (controls = 1.8 ± 0.2 m/s, AM = 2.4 m/s; \( z = 2.61, p = 0.023 \)). For patient MM, peak velocity was significantly lower than controls \( n = 16 \) across all adaptation phases (MM range: 0.8-1.1 m/s; \(-3.35 < z < -2.52, 0.006 < p < 0.045\)) with the exception of prism 1 (controls = 2.0 ± 0.4 m/s, MM = 1.2 m/s; \( z = -2.03, p = 0.069 \)) and prism 6 (controls = 1.7 ± 0.2 m/s, MM = 1.2 m/s; \( z = -1.86, p = 0.090 \)). Overall, movement speed was relatively constant for each patient, with patients MS and AM having no or few significant differences in peak velocity compared to controls, while patient MM showed reduced peak velocity.

Spatial hand paths of the DA showing prismatic effects can be seen in Figure 5. From this it can be seen that when control participants (Figure 5A) and patients (Figure 5B-D) wore rightward-
deviating prisms, the first trial with the prisms (prism 1) was deviated rightward compared to baseline, often with late online corrections toward the target. This also appears on Figure 6, which shows initial movement direction for each experimental trial. The ANOVA of controls’ initial movement direction showed no significant group effect ($F_{1, 14} = 0.75, \eta^2_p = 0.05, p = 0.402$) or interaction ($F_{15, 210} = 1.13, \eta^2_p = 0.08, p = 0.332$), and a significant effect of phase ($F_{15, 210} = 35.5, \eta^2_p = 0.72, p < 0.001$) with Tukey post-hoc analysis revealing significant deviations on prism 1 compared to baseline (baseline = $-0.2 \pm 3.1^\circ$, prism 1 = $10.3 \pm 5.3^\circ$, $p < 0.001$) (Figure 7A). Individual 98% confidence interval analysis on initial movement direction showed rightward deviation on prism 1 for 14/16 controls with 2/16 controls not significantly deviated.

The same 98% confidence interval analysis revealed significant deviation for patient MS (baseline = $-1.9 \pm 3.1^\circ$, 98% CI [-4.6, 0.9], prism 1 = $19.0^\circ$) (Figure 7B), patient MM (baseline = $3.0 \pm 3.8^\circ$, 98% CI [-0.4, 6.4], prism 1 = $6.8^\circ$) (Figure 7C) and patient AM (baseline = $-1.1 \pm 2.8^\circ$, 98% CI [-1.3, 3.6], prism 1 = $16.1^\circ$) (Figure 7D). All individuals’ quantified prism effects (prism 1 – baseline) are shown in Figure 8A. Crawford’s modified t-test on the prism effect showed no significant differences between controls ($n = 16$) (10.5 ± 5.3 cm) and patient MS (MS = 20.9 cm, $z = 1.95, p = 0.078$), patient MM (MM = 3.8 cm, $z = -1.27, p = 0.239$) or patient AM (AM = 14.9 cm, $z = 0.83, p = 0.433$) (Figure 8B).

The analysis of maximum perpendicular deviation provided further evidence for patients and controls having typical prismatic effects. Individual 98% confidence interval analysis showed that on prism 1, 16/16 controls, and all 3 patients were significantly deviated rightward by the prisms compared to baseline (see Figure 9A for individuals’ prism effects). According to Crawford’s modified t-test, there were no significant differences between the controls’ ($n = 16$) prism effect (controls = 8.3 ± 2.5 cm) and patient MS (MS = 5.9 cm, $z = 0.37, p = 0.410$) or
A classic pattern of error reduction was then observed following the first prism trial with less deviated trajectories on prism trials 2, 3 and 4 (Figure 5). Results from the control group ANOVA on initial movement direction showed a maintained significant deviation on prism 2 compared to baseline (baseline = -0.2 ± 3.1°, prism 2 = 5.4 ± 3.6°, p < 0.001) with this deviation no longer significant on prism 3 (2.7 ± 5.2°, p = 0.212). On an individual level, 14 of the 14 controls perturbed by the prisms on prism 1 were still perturbed on prism 2, 8 controls on prism 3 and 6 controls on prism 4. The number of trials to correct the prismatic perturbation and reduce errors, taken as the first trial to fall within the 98% baseline confidence intervals, was 4.5 ± 2.6 trials [range = 3 to 9 prism trials] on average for controls. Patient MS reduced errors by prism trial 4 (Figure 7B), patient MM by prism 2 (Figure 7C) and patient AM by prism 5 (Figure 7D).

Crawford’s modified t-test showed no significant difference in the number of trials to reduce errors between controls (n = 16) and patients (controls = 4.5 ± 2.6 trials; MS = 4 trials, z = -0.19, p = 0.855; MM = 2 trials, z = -0.96, p = 0.366; AM = 5 trials, z = 0.19, p = 0.854).

Typical leftward deviated trajectories indicating an after-effect were then apparent on the first post movement (post 1) with the DA, despite this trial occurring after the NDA post phase of 30 trials (Figure 5). For the control group (n = 16), an ANOVA on initial movement direction showed that the post 1 trial was significantly deviated compared to baseline (baseline = -0.2 ± 3.1°, post 1 = -10.7 ± 6.6°, p < 0.001; Figure 7A). Individual 98% confidence interval analysis showed significant deviation on post 1 for 16/16 controls, patient MS (baseline = -1.9 ± 3.1°, 98% CI [-4.6, 0.9], post 1 = -13.5°; Figure 7B) and patient AM (baseline = -1.1 ± 2.8°, 98% CI [-1.3, 3.6], post 1 = -14.7°; Figure 7D). The after-effect for patient MM (Figure 5C) was not
significant when analysing initial movement direction (baseline = 3.0 ± 3.8°, 98% CI [-0.4, 6.4],
post 1 = 1.9°; Figure 7C). All individuals’ after-effects (post 1 – baseline) are shown in Figure
8C. Comparison of the patients’ after-effects to controls (n = 16) (-10.5 ± 5.3°) using Crawford’s
modified t-test showed no significant differences for patient MS (MS = -11.7°, z = -0.22, p =
0.789), patient MM (MM = -1.0°, z = 1.77, p = 0.106) or patient AM (AM = -15.9°, z = -1.01, p
= 0.345; Figure 8D).

Analysis of maximum perpendicular deviation provided consistent results to the previous
analysis of initial movement direction, with the exception that the after-effect of patient MM was
significant. Individual 98% confidence interval analysis of post 1 compared to baseline showed
significant after-effects for 16/16 controls and all 3 patients (see Figure 9C for individuals’ after-
effects). Crawford’s modified t-test showed that there were no significant differences in the after-
effect according to maximum perpendicular deviation between the controls (n = 16) (controls = -
5.4 ± 1.3 cm), patient MS (MS = -6.1 cm, z = -0.55, p = 0.596), patient MM (MM = -3.8 cm, z =
1.22, p = 0.255) or patient AM (AM = -5.9 cm, z = -0.40, p = 0.693) (Figure 9D). Overall, these
results indicate that all controls and all 3 patients were deviated rightward by the prisms, showed
a typical pattern of error reduction during prism exposure and had characteristic leftward
deviating after-effects.
Transfer of prism adaptation to the non-dominant arm

Interlimb transfer of sensorimotor adaptation was assessed by comparing reaching movements performed with the NDA immediately before (baseline phase) and immediately after (post 1 trial) the prism phase performed with the DA. For controls \((n = 16)\), a 2x2 ANOVA on peak velocity including 2 groups and 2 phases showed that peak velocity did not significantly differ across the different phases (baseline average = 1.7 ± 0.2 m/s, post 1 = 1.8 ± 0.2 m/s, \(F_{1,14} = 0.28, \eta^2_p = 0.02, p = 0.608\)). No significant group effect (\(F_{1,14} = 0.57, \eta^2_p = 0.04, p = 0.462\)) or interaction (\(F_{1,14} = 0.60, \eta^2_p = 0.04, p = 0.453\)) were found. Comparison of NDA peak velocities on post 1 between controls \((n = 16)\) and patients showed that patient MS had no significant difference in peak velocity compared to controls, patient AM had increased peak velocity and patient MM had reduced peak velocity (controls = 1.8 ± 0.2 m/s; MS = 1.6 m/s; \(z = -0.87, p = 0.407\); AM = 2.3 m/s, \(z = 2.81, p = 0.016\); MM = 0.9 m/s, \(z = -4.25, p < 0.001\)), consistent with previously reported results.

Figure 10 shows NDA trajectories for three example controls (Figure 10A) and the three patients (Figure 10B-D). Figure 10 shows that the post 1 movement of the NDA appeared deviated compared to the baseline trajectory for the majority of controls as well as patients, with three apparent patterns of transfer: initial rightward deviation, initial leftward deviation or no transfer. A 2x2 ANOVA on initial movement direction including 2 groups and 2 phases (baseline average and post 1) showed a significant effect of phase, with the post 1 initial movement direction significantly differing from baseline (baseline average = 0.6 ± 3.1°, post 1 = -3.3 ± 6.9°, \(F_{1,14} = 9.53, \eta^2_p = 0.40, p = 0.008\); Figure 11A). No significant group effect (\(F_{1,14} = 0.45, \eta^2_p = 0.03, p = 0.514\)) or interaction (\(F_{1,14} = 2.10, \eta^2_p = 0.13, p = 0.169\)) were found. Individual 98% confidence interval analysis of initial movement direction revealed significant interlimb transfer for 11/16
controls (10 leftward, 1 rightward) and no significant transfer for 5/16 controls, rightward transfer for patient MS (baseline average = 1.7 ± 2.3°, 98% CI [-0.7, 4.0], post 1 = 9.0°; Figure 11B), leftward transfer for patient MM (baseline average = 0.2 ± 2.8°, 98% CI [-2.7, 3.1], post 1 = -6.8°; Figure 11C) and leftward transfer for patient AM (baseline average = -3.7 ± 2.2°, 98% CI [-5.9, -1.4], post 1 = -10.2°; Figure 11D). Individuals’ magnitude of transfer (post1 – baseline) can be seen in Figure 12A. According to Crawford’s modified t-test, absolute interlimb transfer did not significantly differ between any of the patients and the control group (n = 16) (controls = 4.9 ± 4.2°; MS = 7.3°, z = 0.57, p = 0.583; MM = 6.6°, z = 0.39, p = 0.698; AM = 7.0°, z = 0.49, p = 0.638; Figure 11B). We also compared the magnitude of interlimb transfer of each patient to the controls who were classified as presenting interlimb transfer (n = 11). No significant difference was found in the absolute magnitude of transfer between these controls and patients using Crawford’s modified t-test (controls = 6.6 ± 4.0°; MS = 7.3°, z = 0.18, p = 0.865; MM = 6.6°, z = -0.01, p = 0.994; AM = 7.0°, z = 0.10, p = 0.929). Finally, a 2x2 ANOVA (2 Groups, 2 Arms) on the post 1 trials (absolute values) showed a significant effect of arm (F$_{1,14}$ = 13.08, $\eta_p^2$ = 0.48, p = 0.003), with a significantly greater deviation of the dominant arm than the non-dominant arm. There was no significant group or interaction effect. Correlation analysis performed between the control groups’ after-effect on the dominant arm (-10.5 ± 5.3°) and transfer effect on the non-dominant arm (4.9 ± 4.2°) showed no significant correlation (r = -0.27, p = 0.922) (see Figure 6 for graphical presentation of the post values for controls and each patient). These results suggest that the magnitude of each individual’s after-effect and transfer effect were not related.

Results were further confirmed by analysis of maximum perpendicular deviation, as individual 98% confidence interval analysis showed significant interlimb transfer for the majority of
controls, 13/16, and all 3 patients. Crawford’s modified t-test showed no significant differences in the absolute magnitude of transfer between controls and patients (controls = 3.0 ± 1.8 cm; MS = 1.9 cm, $z = -0.63$, $p = 0.549$; MM = 2.8 cm, $z = -0.12$, $p = 0.828$; AM = 4.2 cm, $z = 0.64$, $p = 0.539$). Comparison of patients to controls classified as presenting interlimb transfer ($n = 13$) also showed no significant differences in the absolute magnitude of transfer using Crawford’s modified t-test (controls = 3.5 ± 1.7 cm; MS = 1.9 cm, $z = -0.95$, $p = 0.377$; MM = 2.8 cm, $z = -0.40$, $p = 0.706$; AM = 4.2 cm, $z = 0.42$, $p = 0.693$). These results indicate that all 3 patients transferred the DA adaptation to the NDA despite their corpus callosum abnormalities.
We aimed to determine the role of the corpus callosum in interlimb transfer of sensorimotor adaptation in the context of unconstrained arm movements. Longstanding theoretical models of the neural mechanisms underlying interlimb transfer of motor learning highlighted the corpus callosum as a key structure mediating interhemispheric transfer of motor skills (Parlow and Kinsbourne, 1990; Taylor and Heilman, 1980). While certain studies have provided evidence towards these models (Bonzano et al., 2011; de Guise et al., 1999; Perez et al., 2007a), others have given evidence against (Criscimagna-Hemminger et al., 2003; Thut et al., 1997). Here, we found interlimb transfer of prism adaptation from the dominant arm to the naïve non-dominant arm on an arm reaching task in three corpus callosum patients, with no significant difference in terms of magnitude compared to controls. The presence of interlimb transfer in each patient suggests that on an arm reaching task, interlimb transfer of prism adaptation does not require intact callosal pathways, notably those between bilateral motor, premotor and supplementary motor areas. This would primarily suggest that the dominant theories of interlimb transfer involving the corpus callosum, developed mostly based on distal tasks, may not generalize to other tasks such as proximo-distal arm reaching. Further work is necessary to determine whether interlimb transfer relies on such pathways in healthy individuals. For instance, it is possible that the same neural mechanisms underly interlimb transfer in patients and healthy participants. On the other hand, the underlying mechanisms may differ, whereby the midbody of the corpus callosum may mediate interlimb transfer in healthy controls, whereas in the patients, brain plasticity mechanisms may have resulted in alternative neural mechanisms which maintain apparently normal profile interlimb transfer at the behavioral level.
Comparable motor control and adaptation between corpus callosum patients and controls

Overall, in baseline reaching performance, patient MS, with recent stroke-induced lesions to the corpus callosum (preserving only the genu and splenium), and patient AM, with corpus callosum agenesis, showed few significant differences to controls. The only patient presenting substantial differences compared to controls was patient MM, who had recent stroke-induced lesions to the corpus callosum (preserving only the splenium). For instance, patient MM had no significant differences in initial movement direction and end point accuracy compared to controls, but showed abnormally slowed temporal kinematics, with a reduced peak velocity for both arms. Detrimental effects on temporal movement features such as slowing of unimanual arm reaching have been related to the degradation of corpus callosum pathways connecting premotor areas in stroke patients (Stewart et al., 2017). In addition, patient MM was tested only 5 months post-injury, which could have contributed to this motor slowing. Despite this, we did not find any significant difference between each patient and controls for spatial performance in baseline.

Each patient had a significant rightward prism effect and was able to reduce initial reaching errors caused by the initial perturbation. When examining early prism exposure, no significant difference between controls and the patients was found for the number of trials to reduce prism-induced errors, with fast error reduction based on visual feedback as in other reaching studies (Gréa et al., 2002; Newport and Jackson, 2006; O’Shea et al., 2014; Pisella et al., 2004; Renault et al., 2020). While awareness of the perturbation and strategic, possibly explicit, processes could partly underlie the rapid error reduction as well as adaptation and transfer, previous research (Mazzoni and Krakauer, 2006; Newport and Jackson, 2006; Taylor et al., 2011; Wang et al., 2011) suggest that this is unlikely to fully account for the present results. Finally, a significant leftward after-effect, often referred to as a hallmark of sensorimotor adaptation, was observed on
the dominant arm across the control group and patients. The after-effect was equivalent to a deviation of -10.5 ± 5.3° for the control group and -11.7° to -15.9° for the two patients with a significant after-effect, MS and AM respectively. The third patient, MM, had a non-significant after-effect of -1° at initial movement direction, but the after-effect was significant when looking at maximum perpendicular deviation. We did not find any significant correlation between the number of trials taken to de-adapt during the post phase and the magnitude of the after-effect, suggesting that the rate of non-dominant arm de-adaptation did not substantially affect the magnitude of the after-effect. The after-effect in our study (10.5°) corresponded to 61.4% of the prismatic deviation (17.1°), which was similar to the after-effect of 60.9% (9.1°) found by Facchin et al. (2019, Experiment 1) who used 15° right-ward deviating prisms over 150 adaptation trials, and, importantly, did not test opposite arm performance prior to after-effect assessment (see also Facchin et al. 2019 – Table 1 for a summary of the after-effects reported in the literature). Our findings thus support the idea of sensorimotor adaptation in each participant, offering the opportunity to assess interlimb transfer in patients and controls.

*Neural mechanisms of interlimb transfer*

We hypothesized that corpus callosum abnormalities would interfere with interlimb transfer yet found interlimb transfer in each patient with either extensive midbody lesions or complete agenesis. Further, we found no significant difference in the magnitude of absolute interlimb transfer between each patient and matched controls. Across controls and patients, we did observe two profiles of interlimb transfer to the non-dominant arm: the majority with initial leftward deviation (opposite to the prismatic perturbation), consistent with encoding in extrinsic
coordinates, and a few participants with initial rightward deviation (in the same direction as the prismatic perturbation), consistent with encoding in intrinsic coordinates. Overall, these findings support and extend those found on young, healthy individuals (Kalil and Freedman, 1966; Renault et al., 2020).

Regarding the underlying neural mechanisms of interlimb transfer, one could argue that the transfer observed in each patient could be due to the development of compensatory interhemispheric pathways through brain plasticity. Agenesis patients, like patient AM, often have preserved interhemispheric communication linked to the formation of alternative interhemispheric networks or upregulated information transfer via posterior or anterior commissures (Brescian et al., 2014; Tovar-Moll et al., 2014; Van Meer et al., 2016). In other pathologies such as split-brain patients, the presence and timeline of recovery of interhemispheric connectivity due to brain plasticity is less clear (for a review, see Mancuso et al., 2019). In studies on split-brain patients, recovery of interhemispheric connectivity was shown 2-7 years post-surgery in a group of patients (Roland et al., 2017), and decades post-surgery in two separate case studies (Nomi et al., 2019; Uddin et al., 2008). Here, we tested two stroke patients (MM and MS) within 5 months and 2 years post-injury, respectively. This short timescale reduces the likelihood of interhemispheric connectivity changes due to plasticity. Further, both patients had non-surgical, stroke-induced lesions following a normal development with no history of epilepsy, removing potential confounds of studying a surgically split brain due to severe epilepsy. While patient AM could have developed compensatory mechanisms for interlimb transfer during development, this explanation would be less likely for patient MS and patient MM.

One possibility is that preserved corpus callosum splenium fibres in patients MM and MS could underlie interlimb transfer. The splenium is known to connect bilateral posterior parietal,
temporal and visual areas (Putnam et al., 2009; Zarei et al., 2006), areas known to contribute to reach adaptation. In particular, posterior parietal areas underlie the planning and control of visually guided arm movements (Buneo and Andersen, 2006) while both posterior parietal and visual areas have been implicated in prismatic adaptation (Clower et al., 1996; Crottaz-Herbette et al., 2014; Luauté et al., 2009; Magnani et al., 2013; Pisella et al., 2005). While bilateral motor and premotor transcallosal connections were disrupted in patients MM and MS, it is possible that splenial connections could mediate transcallosal mechanisms of interlimb transfer between bilateral posterior parietal, temporal or visual cortex areas. In line with this, in an agenesis patient like patient AM, visual areas normally connected via the splenium, were shown instead to be connected via the anterior commissure (Van Meer et al., 2016). Further work, for instance on other patients with rare stroke types affecting specifically the corpus callosum, and in particular the splenium, would thus be necessary to test this hypothesis.

An alternative hypothesis is that the observed interlimb transfer does not in fact rely on interhemispheric transfer and instead involves the dominant hemisphere (contralateral to the trained dominant arm). Indeed, pioneering work on the neural basis of interlimb transfer (Taylor and Heilman, 1980) proposed that, for right-handed participants, the left hemisphere contains the effector-independent motor engram formed during learning. More recent research has further confirmed the implication of dominant left hemisphere networks in both motor control and adaptation with the right arm in right-handers (Buneo and Andersen, 2006; Dassonville et al., 1997; Luauté et al., 2009; Pool et al., 2014), including adaptation to rightward prisms (Panico et al., 2020; Schintu et al., 2020). Further, left hemisphere, but not right hemisphere, stroke patients show impaired adaptation to visuomotor rotations (Mutha et al., 2011). It is thus possible that the updated motor plans stored within the dominant hemisphere are accessible to the dominant limb
but also the non-dominant limb, via ipsilateral cortico-spinal pathways rather than callosal pathways. Neurophysiological findings in healthy human and non-human primates have shown, for instance, that not only the contralateral hemisphere, but also the ipsilateral hemisphere can contribute to the execution of unimanual movements (Ames and Churchland, 2019; Anguera et al., 2007; Gabitov et al., 2016; Heming et al., 2019; Lee et al., 2010; Luauté et al., 2009). This is supported by clinical studies showing that unilateral stroke damage can affect the contralateral arm but also the ipsilateral arm (Desrosiers et al., 1996; Hermsdörfer et al., 1999; Schaefer et al., 2009) especially on proximal tasks (Jones et al., 1989). The role of ipsilateral descending pathways, comprising around 10-15% of all descending motor pathways to upper and lower arm extremities, is currently under intense investigation in both motor control and stroke rehabilitation research of the upper limb (Bradnam et al., 2013; Duque et al., 2008). Ipsilateral pathways appear to contribute more to proximal compared to distal effectors (Bawa et al., 2004; Chen et al., 2003; Müller et al., 1997; Turton et al., 1996), a finding which may be linked to reports that interlimb transfer is greater on proximal compared to distal tasks (Aune et al., 2017; Thut et al., 1997). Further, Criscimagna-Hemminger et al. (2003) showed interlimb transfer of force-field adaptation in a split-brain patient on a constrained proximo-distal reaching task, suggesting that such interlimb transfer does not rely on the corpus callosum and could be mediated by ipsilateral descending pathways. Studies finding interlimb transfer on distal (hand or finger) tasks, such as sequence learning or force tasks, however, implicate a key role of interhemispheric communication via the corpus callosum (Bonzano et al., 2011; Gabitov et al., 2016; Lee et al., 2010; Perez et al., 2007a; Ruddy and Carson, 2013). These results correspond to motor control observations in our patients, and other patients with corpus callosum abnormalities, showing that proximo-distal arm reaching performance can be largely unaffected
while distal motor tasks are impaired (Gordon et al., 1971; Sauerwein and Lassonde, 1994). These findings, in combination with our results obtained on an unconstrained proximo-distal reaching task, could suggest that tasks involving distal effectors could require callosal pathways, while tasks involving proximal effectors could rely on ipsilateral descending pathways.

One final interpretation could be that subcortical structures such as the cerebellum could underlie this interlimb transfer. Day and Brown (2001) suggested that visuomotor integration of reaching movements involved subcortical regions, potentially the cerebellum, as an agenesis patient showed normal visuomotor reaching despite an absent corpus callosum and absent ipsilateral motor evoked responses to the lower arm muscles. Since, imaging studies have shown evidence for cerebellar recruitment in prismatic adaptation involving reaching movements (Küper et al., 2014; Luauté et al., 2009). Notably, rightward prismatic adaptation, shown to involve a dominantly left lateralized cortical network, also involves the subcortical contralateral right cerebellum (Panico et al., 2020; Schintu et al., 2020), reciprocally connected to left cortical areas including parietal and motor cortices (Kamali et al., 2010; Palesi et al., 2017). A wealth of cerebellar patient studies have also shown the role of the cerebellum in force-field and visuomotor adaptation (Donchin et al., 2012; Rabe et al., 2009; Smith and Shadmehr, 2005), and prism adaptation (Block and Bastian, 2012; Hanajima et al., 2015; Martin et al., 1996b; Pisella et al., 2005). However, while the cerebellum has been shown to play a role in adaptation, Block and Celnik (2013) showed that inhibitory cerebellar stimulation did not interfere with interlimb transfer, and only interfered with visuomotor adaptation. Contrarily, on a grasping task, Nowak et al. (2009) showed impaired interlimb transfer in cerebellar patients. As cerebellar contributions vary between different adaptation tasks (Donchin et al., 2012; Rabe et al., 2009), and given that different adaptation paradigms are not necessarily measuring the same process
(Fleury et al., 2019), further work is necessary to determine whether interlimb transfer of prismatic adaptation is mediated by cerebellar mechanisms, involved in a parieto-cerebellar-motor network (Newport and Jackson, 2006; Obayashi, 2004).

In summary, our assessment of arm reaching performance in patients with corpus callosum abnormalities revealed interlimb transfer of prismatic adaptation, with no significant differences in the magnitude of transfer compared to matched controls. The presence of interlimb transfer in each patient suggests that on an arm reaching task, interlimb transfer of prism adaptation does not require intact callosal pathways, notably those between bilateral motor, premotor and supplementary motor areas. This would primarily suggest that the dominant theories of interlimb transfer involving the corpus callosum, developed mostly based on distal tasks, may not generalize to other tasks such as proximo-distal arm reaching. Further work is necessary to determine whether interlimb transfer relies on such pathways in healthy individuals. For instance, it is possible that the same neural mechanisms underly interlimb transfer in patients and healthy participants. On the other hand, the underlying mechanisms may differ, whereby the midbody of the corpus callosum may mediate interlimb transfer in healthy controls, whereas in the patients, brain plasticity mechanisms may have resulted in alternative neural mechanisms which maintain an apparently normal profile of interlimb transfer at the behavioral level.
Limitations

One possible limitation of the present study is that brain plasticity in corpus callosum patients could have resulted in alternate pathways for interlimb transfer of sensorimotor adaptation, which could otherwise rely on the midbody of the corpus callosum in a normal healthy brain. This limitation could be especially relevant for the agenesis patient as previous studies on agenesis subjects have shown upregulated functionality of the anterior commissure (Brescian et al., 2014; Tovar-Moll et al., 2014; Van Meer et al., 2016), ipsilateral descending pathways (Ziemann et al., 1999), and possibly subcortical pathways (Day and Brown, 2001). Further studies using functional brain imaging or brain stimulation would be necessary to give greater insights into the underlying neural mechanisms.

A second limitation is that we were able to work with a relatively small number of patients. This is because there is a low prevalence of agenesis and callosal lesions in stroke patients (Giroud and Dumas, 1995; Paul et al., 2007; Sun et al., 2019). For example, stroke confined to the corpus callosum was observed in 21 of 5584 patients (0.4%) in the Shanghai study with a recruitment period of 4 years (Sun et al., 2019), and 3 of 282 patients (1%) in the French study with a recruitment period of 1 year (Giroud and Dumas, 1995). However, previous research has shown that even only one rare patient can be enough to reveal key insights in neuroscience, as evidenced by the Nobel-prize winning research on split-brain developed by Sperry and colleagues (Gazzaniga et al., 1962; Volz and Gazzaniga, 2017). Increasing sample size would not change our observations of interlimb transfer on all three patients, and thus our conclusion, that the midbody of the corpus callosum is not necessary for the interlimb transfer of prism adaptation. However, working with more patients, and especially patients with distinct lesions, would be helpful in clarifying the neural mechanisms underlying interlimb transfer. This is consistent with the idea that heterogenous samples can give greater neurological insights (Martin et al., 1996; Willems et al., 2014). Interestingly, while Sun et al. (2019) found high prevalence of splenium lesions, we, along with Giroud and Dumas (1995),
found a preserved splenium in both stroke patients. A future study with patients presenting splenium lesions would be useful to test the hypothesis that interlimb transfer relies on interhemispheric transfer of information via the splenium.

Finally, the two stroke patients and the agenesis patient tested in our study were heterogeneous in terms of laterality, sex and age, giving rise to a heterogeneous control group. However, age characteristics did not appear to influence the results of visuomotor adaptation and interlimb transfer across participants. Further, on a similar prismatic adaptation study, no significant effect of laterality or sex was found in a larger group of control participants which was more homogenous in terms of age (Renault et al., 2020). Whilst we used adapted statistical analyses developed to estimate whether a single patient can be considered normal or abnormal compared to small or moderate control samples (Crawford et al., 2010; Crawford and Garthwaite, 2007), statistically non-significant results do not necessarily indicate complete lack of difference between patients and controls (Altman and Bland, 1995). Further studies with an increased number of control participants could be useful to clarify this.
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Figure Legends

Figure 1. Sagittal MRI cross-section spanning from right (top row) to left (bottom row) hemisphere for A. A typical control participant with complete corpus callosum (T1) B. Patient MS who had a brain aneurysm rupture causing lesions to the corpus callosum with only the genu (g) and splenium (s) preserved (T2-flair) C. Patient MM who had a stroke causing lesions to the corpus callosum with only the splenium (s) preserved (T1) and D. Patient AM with absent corpus callosum since birth (complete callosal agenesis) (T1). Corpus callosum regions marked by white arrows are labelled on the middle row images, based on Witelson (1989), as: rostrum (r), genu (g), anterior midbody (am), central midbody (cm), posterior midbody (pm), isthmus (i) and splenium (s).

Table 1. Clinical and MRI features for each patient based on neuropsychological assessments. Columns indicate clinical features of disconnection which were either present (+) or absent (o) in each patient, with indication of the affected arm – left (L) or right (R) when applicable. Square brackets [ ] are used to report when symptoms were only mild or the frequency of Alien Hand episodes. *Alien hand episodes for Patient MS were present immediately following the stroke, but resolved 6 months post-stroke, reoccurring only with fatigue or stress. MRI features indicate lesioned (black) and preserved (white) areas of the corpus callosum; a cross indicates complete absence of the corpus callosum from birth.

Figure 2. Experimental protocol, with 3 phases (baseline, prism, and post-phase) made up of blocks of dominant or non-dominant arm reaching. In the baseline phase, participants reached
under normal vision from the starting point (black plus +) to one of three flashed visual targets (grey-white circles) 30 times with the dominant arm, then 30 times with the non-dominant arm (totaling 10 trials per target per arm). In the following prism phase (exposure), participants reached 100 times (Control group A, patient MS, patient AM) or 50 times (Control group B, patient MM) with the dominant arm towards the middle, straight-ahead visual target while wearing rightward deviating (17°) prismatic goggles. During the post phase, participants again reached under normal vision to one of three visual targets, 30 times with the non-dominant arm, then 30 times with the dominant arm (totaling 10 trials per target per arm).

Figure 3. Baseline phase top-down view of the 10 reaching hand paths toward the middle straight-ahead target (red circle) for the dominant arm (DA) and non-dominant arm (NDA) for A. An example control B. Patient MS C. Patient MM and D. Patient AM. Peak velocity is indicated with a black star.

Figure 4. Baseline kinematics for the dominant arm (DA) and non-dominant arm (NDA) movements to the middle straight-ahead target A. Initial Movement Direction B. Final Movement Direction C. End Point Accuracy D. Max Perpendicular Deviation E. Peak Velocity F. Time to Peak Velocity G. Movement Time and H. Reaction Time. Data are shown for the control group (n = 16) average (white circles with standard deviation error bars) and individual average values for controls (grey dashed circles), patient MS (triangles), patient MM (diamonds) and patient AM (squares). Significant differences between the control group DA and NDA, according to a 2x2 (Arm x Group) ANOVA, are marked with spanning black asterisks. For each
arm, significant differences between a patient and the control group, according to Crawford’s modified t-test, are indicated by black asterisks with corresponding patient initials (MS - patient MS, MM - patient MM, AM - patient AM). *p value < 0.05, ***p value < 0.01.

**Figure 5.** Prism-exposed dominant arm top-down view of hand paths toward the target (red circle) for A. An example control B. Patient MS C. Patient MM and D. Patient AM. Trajectories include: a baseline phase representative trial (black), prism trials 1 (red), 2 (dark orange), 3 (light orange) and 4 (yellow), and the post 1 trial (blue). The blue dashed line in panel D. is the estimated post 1 trial trajectory for patient AM calculated based on motion tracking of a standard video-camera recording using imageJ manual tracking software and adjustment according to a standard baseline velocity profile, as a technical issue on this trial caused kinematic data loss via the Codamotion system. Occurrence of peak velocity for each trial is marked with a black star; occurrence of maximum perpendicular deviation is marked with a white star.

**Figure 6.** Initial movement direction for both the dominant arm (DA, represented as black filled symbols), and non-dominant arm (NDA, represented as white filled symbols) across movements toward the middle target for A. The control group (n = 16) average values (circles) B. Patient MS (grey triangles) C. Patient MM (light grey diamonds) D. Patient AM (dark grey squares). Data shown include: all 10 individual baseline trials toward the middle target (DA then NDA), prism trials 1-50 toward the middle target (DA only), and all 10 individual post trials toward the middle target (NDA then DA). Error bars in panel A. represent standard deviations of the control group mean. The post 1 value for patient AM in panel D. was calculated from an estimated trajectory
created using imageJ motion tracking of a standard video-recording and adjustment according to a standard baseline velocity profile, as Codamotion kinematic data were lost due to a technical issue on this trial.

**Figure 7.** Prism-exposed dominant arm initial movement direction across trials for A. The control group (n = 16) showing group average (white circles) and individual values (light grey circles) B. Patient MS (grey triangles) C. Patient MM (light grey diamonds) D. Patient AM (dark grey squares). Data shown include: baseline (10 trial average), prism trials 1 to 10, the last 10 prism trials average (prism 41-50) and the post1 trial. Error bars in panel A. represent control group standard deviations, asterisks indicate trials which significantly differ to baseline according to a 2x16 (Group x Phase) ANOVA. Error bars in panels B-D. represent the individual patient standard deviations for baseline (10 trials) and the last common prism phase (10 trials), asterisks indicate trials which significantly differ from the baseline average according to baseline 98% confidence interval analysis. All asterisks are indicated at the threshold **p value < 0.02.

The post 1 value for patient AM in panel D. was calculated from an estimated trajectory created using imageJ motion tracking of a standard video-recording and adjustment according to a standard baseline velocity profile, as Codamotion kinematic data were lost due to a technical issue on this trial.

**Figure 8.** Prismatic effects and after-effects for each individual, quantified with initial movement direction analysis. Panels A. and C. show initial movement direction across trials for all individual controls (grey circles), patient MS (grey triangle), patient MM (light grey diamond)
and patient AM (dark grey square), calculated as the difference between each individual’s baseline average and the individual’s prism 1 or post 1 trial respectively. Notations below the graphs indicate patient initials (MM, MS, MM) and control references (C1-C8) for each corresponding group (Group A: 52 ± 4 years-old, 100 prism trials; Group B: 29 ± 4 years-old, 50 prism trials). The grey dashed lines mark the control group average, ns. indicates individuals for whom the effect was not significant according to the individual’s baseline 98% confidence interval analysis. Panels B. and D. show the data in panels A. and C. respectively, with control data represented by the control group average and standard deviation. Asterisks in panels B. and D. indicate significant differences between the patients and the control group according to Crawford’s modified t-test. *p value < 0.05, ***p value < 0.01. The post 1 value for patient AM in panels C. and D. was calculated from an estimated trajectory created using imageJ motion tracking of a standard video-recording and adjustment according to a standard baseline velocity profile, as Codamotion kinematic data were lost due to a technical issue on this trial.

**Figure 9.** Prism effects and after-effects for each individual, quantified based on maximum perpendicular deviation analysis. Panels A. and C. show the quantified effect values according to maximum perpendicular deviation across all individual controls (grey circles), patient MS (grey triangle), patient MM (light grey diamond) and patient AM (dark grey square), calculated as the difference between each individual’s exposed dominant arm baseline average and prism 1 or post 1 trial respectively. Notations below the graphs indicate patient initials (MM, MS, MM) and control references (C1-C8) for each corresponding group (Group A: 52 ± 4 years-old, 100 prism trials; Group B: 29 ± 4 years-old, 50 prism trials). The grey dashed lines mark the control group average, ns. indicates individuals for whom the effect was not significant according to the
individual’s baseline 98% confidence interval analysis. Panels B. and D. show the data in panels A. and C. respectively, with control data represented by the control group average and standard deviation. Asterisks in panels B. and D. indicated significant differences between the patients and the control group according to Crawford’s modified t-test. *p value < 0.05, ***p value < 0.01. The post 1 value for patient AM in panels C. and D. was calculated from an estimated trajectory created using imageJ motion tracking of a standard video-recording and adjustment according to a standard baseline velocity profile, as Codamotion kinematic data were lost due to a technical issue on this trial.

**Figure 10.** Naïve non-dominant arm top-view of hand paths for a baseline representative trial (black) and the post 1 trial (blue) for A. Three example controls showing leftward, rightward or no initial deviation on the post 1 trial compared to baseline B. Patient MS showing an initial rightward deviation C. Patient MM showing an initial leftward deviation and D. Patient AM showing an initial leftward deviation. Occurrence of peak velocity is marked with a black star; occurrence of maximum perpendicular deviation is marked with a white star.

**Figure 11.** Naïve non-dominant arm initial movement direction before and after prismatic adaptation with the dominant arm for A. The control group (n = 16) showing the group average (white circles) and individual values (grey circles) B. Patient MS (grey triangles) C. Patient MM (light grey diamonds) D. Patient AM (dark grey squares). Data show the baseline 10 trial average and post 1 trial. Error bars in panel A. represent control group standard deviations, and asterisks indicate trials which significantly differ to baseline according to a 2x2 (Group x Phase) ANOVA.
Error bars in panels B.-D. represent each patient’s baseline standard deviations, and asterisks indicate trials which significantly differ from the baseline average according to baseline 98% confidence interval analysis. Significance is shown at **p value < 0.02 threshold.

Figure 12. Interlimb transfer for each individual, quantified with initial movement direction analysis. Panel A. shows the interlimb transfer values according to analysis of initial movement direction for all individual controls (grey circles), patient MS (grey triangle), patient MM (light grey diamond) and patient AM (dark grey square), calculated as the difference between each individual’s naïve non-dominant arm baseline average and post 1 trial. Notations below the graphs indicate patient initials (MM, MS, MM) and control references (C1-C8) for each corresponding group (Group A: 52 ± 4 years-old, 100 prism trials; Group B: 29 ± 4 years-old, 50 prism trials). The grey dashed lines mark the control group average, ns. indicates individuals for whom the effect was not significant according to the individual’s baseline 98% confidence interval analysis. Panel B. shows the absolute transformation of the data in panel A. with control data represented by the control group average and standard deviation. Asterisks in panel B. indicated significant differences between the patients and the control group according to Crawford’s modified t-test. *p value < 0.05, ***p value < 0.01.
Figure 2. 

Baseline phase

Dominant Arm  Non-Dominant Arm

Prism phase

Dominant Arm

Post phase

Non-Dominant Arm  Dominant Arm
Figure 3.

A  Example Control

B  Patient MS

C  Patient MM

D  Patient AM

10cm  10cm

- Target
- Baseline Trials
- Peak Velocity
Figure 4.
A. Initial Movement Direction
B. Final Movement Direction
C. End Point Accuracy
D. Maximum Perpendicular Deviation
E. Peak Velocity
F. Time to Peak Velocity
G. Movement Time
H. Reaction Time

Legend:
- Control Group (n=16)
- Individual Controls
- Patient MS
- Patient MM
- Patient AM
Figure 5.

A  Example Control

B  Patient MS

C  Patient MM

D  Patient AM

Legend:

- Target
- Baseline Example Trial
- Prism 1 Trial
- Prism 2 Trial
- Prism 3 Trial
- Prism 4 Trial
- Post 1 Trial
- Peak Velocity
- Maximum Perpendicular Deviation
Figure 6.

A - Control Group

Baseline | Prism Phase | Post
---|---|---
DA | NDA | DA

B - Patient MS

Baseline | Prism Phase | Post
---|---|---
DA | NDA | DA

C - Patient MM

Baseline | Prism Phase | Post
---|---|---
DA | NDA | DA

D - Patient AM

Baseline | Prism Phase | Post
---|---|---
DA | NDA | DA
Figure 8.

A  Individual Prism Effects

B  Prism Effects

C  Individual After-Effects

D  After-Effects
Figure 10.

A
Example Controls
Left-ward Transfer
No Transfer
Right-ward Transfer

B
Patient MS
Right-ward Transfer

C
Patient MM
Left-ward Transfer

D
Patient AM
Left-ward Transfer

Legend:
- Target
- Baseline Example Trial
- Post 1 Trial
- Peak Velocity
- Maximum Perpendicular Deviation

10cm
10cm
Figure 11.
Figure 12.

A  Individual Interlimb-Transfer Values

B  Absolute Interlimb-Transfer Values

Angular Deviation (°)

Reference Group

C3  C2  C4  C6  C1  C7  C5  C8  C4  C6  C5
A   A   B   A   B   A   B   A   B   B   A

NS, NS, NS, NS, NS

Controls  MS  MM  AM
Table 1. Clinical and MRI features of callosal lesions

| Patients | Proprioceptive transfer (Weeks) | Visual agnosia (R) | Visual agnosia (L) | Tactile anomia (L) | Agraphia (L) | Constructive apraxia (L) | Ideomotor apraxia (L) | Aliens Hand (Diagnosis) | MRI features |
|----------|--------------------------------|-------------------|--------------------|-------------------|--------------|--------------------------|----------------------|------------------------|---------------|
| MS stroke-induced lesions | +                             | o                 | o                  | o                 | o            | + (L) [mild]             | + (R) *               |                       |               |
| MM stroke-induced lesions | +                             | o                 | o                  | + (L)             | + (R)        | + (L)                   | + (R) [mild]          |                       |               |
| AM agenesis | +                             | + (R) [mild]     | o                  | + (R)             | + (L)        | + (R)                   | + (L) [mild]          | + (R) [weekly]        | ×             |

Columns indicate clinical features of disconnection (based on neuropsychological assessments) which were either present (+) or absent (o) in each patient, with indication of the affected arm – left (L) or right (R) when applicable. Square brackets [ ] are used to report when symptoms were only mild or the frequency of Alien Hand episodes. *Aliens hand episodes for Patient MS were present immediately following the stroke, but resolved 6 months post-stroke, reoccurring only with fatigue or stress. MRI features indicate lesioned (black) and preserved (white) areas of the corpus callosum; a cross indicates complete absence of the corpus callosum from birth.