Limitations of compensatory plasticity: the organization of the primary sensorimotor cortex in foot-using bilateral upper limb dysplasics

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Abstract

What forces direct brain organization and its plasticity? When a brain region is deprived of its input would this region reorganize based on compensation for the disability and experience, or would strong limitations of brain structure limit its plasticity? People born without hands activate their sensorimotor hand region while moving body parts used to compensate for this ability (e.g. their feet). This has been taken to suggest an organization based on functions, such as performing manual-like dexterous actions, rather than on body parts. Here we test the selectivity for functionally-compensatory body parts in the sensorimotor cortex of people born without hands. Despite clear compensatory foot use, the sensorimotor hand area in the dysplasic subjects showed preference for non-compensatory body parts whose cortical territory is close to the hand area. This suggests that function-based organization, originally proposed for full congenital blindness and deafness, does not apply to cases of the primary sensorimotor cortex in dysplasia. This is consistent with the idea that experience-independent functional specialization occurs at relatively high levels of representation. Furthermore, it stresses the roles of neuroanatomical constraints such as topographical proximity and connectivity in determining the functional development of brain regions. These findings reveal limitations to brain plasticity and to the role of experience in shaping the functional organization of the brain.

Introduction

What determines the role of brain regions, and their plasticity when typical inputs or experience is not provided? To what extent can extreme compensatory use affect brain organization? Or is brain organization limited in its plasticity, due to strong neuroanatomical constraints? The balance between nature and nurture has been a long-standing question in neuroscience.

Here we tackle this question using the model of limb loss, in the sensorimotor cortex of upper limb dysplasic individuals, born without hands. What would take the place of the missing hands? Several recent studies stress the role of experience-based plasticity, and claim that this region reorganizes to support the use of other body parts to perform everyday actions. People born without hands showed activation of the hand sensorimotor cortex for body parts used to "replace" congenitally missing hands, be it the feet (Stoeckel et al., 2009) or other, multiple body parts (in addition to the remaining hand, in congenital one-handers; (Hahamy et al., 2017). In the somatosensory cortex, the hand responsive area shrinks depending on the size and use of the hand remains (Stoeckel et al., 2005a; Stoeckel et al., 2005b), and foot haptic stimulation activated the lateral sensory cortex (Stoeckel et al., 2004). Furthermore, in two individuals born without hands bilaterally, a study has shown that strong TMS stimulation of the lateral motor cortex generated motor evoked potentials not only in the residual finger or shoulder of the subjects but also in the foot, and interfered with performing a foot motor task (Stoeckel et al., 2009). These findings were interpreted as evidence for robust plasticity of the sensorimotor cortex and functional takeover of the hand area by the feet. Furthermore, they raised the possibility that the primary sensorimotor cortex is functionally-selective rather than selective for topographical body parts, such that the hand area may correspond to any effector that functions as a hand in everyday tasks like grasping and manipulating objects (Hahamy et al., 2017).

However, the *specificity* of such supposed compensatory reorganization (for the body part now used as hands) has not been thoroughly tested. None of the studies tested and showed that the hand area is more activated for compensatorily used body parts than for other proximal, but non-compensatorily used organs. Is the hand sensorimotor cortex indeed selective for compensatorily used body parts? Alternatively, plasticity due to compensatory effector experience may be limited by neuroanatomical constraints such as topographical proximity and connectivity of this brain system, enabling only a takeover by closer cortical territories, akin to what is found in late-onset amputation (Flor et al., 1995; Hall et al., 1990; Pons et al., 1991; Ramachandran et al., 1992).

Here we test these competing hypotheses by mapping sensorimotor responses to movement of various body parts in five individuals born without hands (dysplasic subjects), who use their feet for everyday functions. The implications of the results are discussed in the context of the broader issue of retained functional specialization in congenital blindness and deafness.

Results

To test the specificity of plasticity in the sensorimotor hand area in people born without arms or hands (see **Table 1**), we used an active motor paradigm, designed to activate both primary somatosensory and primary motor cortices, similar to previous studies of reorganization (Foell et al., 2014; Hahamy et al., 2017; Lotze et al., 2001; MacIver et al., 2008; Makin et al., 2015). We scanned five dysplasic subjects, as well as a control group, as they performed simple flexing movements of different parts of their body. The body parts chosen for this experiment included not only the hands (in the controls, to be used as a localizer), but also the feet, which the dysplasic subjects use to overcome their disability. Our study participants, according to self-report, rely largely on their dexterous feet (dominantly their right foot; all were right footed) to perform daily typical manual activities. Their feet are extraordinarily dexterous, allowing them to use cell phones, eating utensils and nearly all other everyday tools (see list at **Table S1**). In a questionnaire of tool use, all the dysplasic subjects reported to use the clear majority of the tools they have used with their lower limbs (see **Fig. S1**). Foot tool-use accounted for a minimum of 92% of the used tools, although a minority of tools were jointly manipulated by the lower face or remaining upper limbs in specific individuals (see **Fig. S1**, **Table 1**). Additionally, we inspected movement of the shoulder and lips, expected to activate neighboring cortical regions on both sides of the missing hand territory, as well as a control body part, which is not an immediate cortical neighbor of the hand nor is it used compensatorily to replace hand function: the abdomen.

In the control group, this protocol resulted in a typical somatotopic activation pattern with sensorimotor responses along a superior-inferior axis for the foot, abdomen, shoulder, hand and lips movements (**Fig. 1A**; hand peak is delineated in white), replicating the known Penfield homunculus (Penfield and Boldrey, 1937). In the dysplasic subjects, though the peak responses remained topographic, movement in every tested body part resulted in some activation in the hand region (**Fig. 1B**). This included also increased activation of the hand area while they moved their right foot, used by these subjects to perform typically manual actions, as reported before. Indeed, plotting the group differences showed that the sensorimotor hand area had stronger activation in the dysplasic subjects than in the controls for moving the various body parts, including the foot (**Fig. 1C**).

When exploring selectivity of sensorimotor responses, plotting the preferential activation per cortical vertex (in a winner-takes-all approach; **Fig. 2A, B**), the dysplasic subjects show a preference for shoulder and abdomen movements in the typical hand area (**Fig. 2B**; hand area delineated white). These patterns were consistent across the individual subjects (**Fig. S2**). We further sampled the response pattern within the hand region-of-interest (ROI; defined by significant overlapping activation for hand movement as compared to baseline in all control subjects). The activation in the dysplasics hand region is strongest for the movement of the shoulder, which is proximal to the missing hand, but is also significant for the abdomen, whereas moving the foot does not generate strong significant activation in the hand area at large (**Fig. 2C**). Despite the preferential compensatory use of the right foot in these subjects to overcome their disability, movements of the foot do not seem to favorably overtake this region. In fact, when contrasting moving the

foot as compared to the non-compensatory but more proximal abdomen, none of the dysplasic subjects show significant activation in their sensorimotor hand area (**Fig. 2D** for probabilistic mapping across subjects; **Fig. S3** for individual subjects).

This does not mean that no foot selectivity exists in these subjects: when directly contrasting foot movement to movement of the abdomen in the dysplasic subjects, activation is found not only in the primary sensorimotor cortex foot region, but also in the superior parietal lobule and posterior superior frontal sulcus. Furthermore, foot selectivity differs between the dysplasics and controls in various brain regions, including in the parietal, frontal and temporal lobes, and also in the sensorimotor hand area itself (**Fig. 2E**). However, the difference in the hand area appears to reflect a higher selectivity in the control group (**Fig. 2F**).

We then inspected if functional connectivity (FC) may reflect use-based plasticity within the primary sensorimotor cortex. Plotting the FC of the hand area with the cortical areas of the other tested body parts shows that no specific increase in preferential connectivity exists in the dysplasics to the foot region (**Fig. 2G**). The hand-foot FC is not the strongest FC pattern from the hand area, nor is it increased beyond the hand-foot FC of the controls. Furthermore, the group differences in FC from the hand area across the entire cortex shows that the deprived hand area does not seem to change greatly (**Fig. 2H, I**; note the Bayes factor values range, suggesting very few regions show even weak evidence for a group difference).

Discussion

We tested people born without hands who use their feet to perform every-day manual tasks. We found that their sensorimotor hand area is activated by foot movements more than in typically developed control subjects (**Fig. 1**), replicating previous findings (Hahamy et al., 2017; Stoeckel et al., 2004; Stoeckel et al., 2009). However, in contrast to previous research, we additionally tested for the selectivity of the compensatorily-used effector, and found that the hand area shows no foot selectivity. Instead, the hand area is more strongly activated for proximal but non-compensatory body parts, which are not used as effectors, such as the shoulder and abdomen (**Fig. 2**).

Past findings of sensorimotor plasticity in people with congenital hand absence were thought to reflect use-dependent, compensatory plasticity for sensorimotor loss (Hahamy et al., 2017; Stoeckel et al., 2004; Stoeckel et al., 2009). These results were interpreted as evidence that the primary sensorimotor cortex shows functional selectivity for performing tasks typically conducted with the hands, and not necessarily for the specific body part (Hahamy et al., 2017). This interpretation builds upon a model developed based on association sensory cortex organization in congenital blindness and deafness. In these cases, the roles of association sensory cortex regions appear to be defined not by their commonly-driving sensory modality ("visual cortex"), but by their computational role. This was demonstrated in vision (Bi et al., 2016; Bock and Fine, 2014; Heimler et al., 2015; Mahon and Caramazza, 2011; Renier et al., 2014; Ricciardi et al., 2014; Thaler and Goodale, 2016) for domain selectivity for complex perceptual and functional categories, such as objects, body parts and scenes (Mahon and Caramazza, 2011) as well as for functional tasks such as spatial localization (Renier et al., 2014) and motion perception (Ptito et al., 2009), and has been extended also to functional tasks for audition (Bola et al., 2017; Lomber, 2017). Such selectivity is retained, albeit via different sensory inputs, even in the absence of original dominant sensory experience. The finding of similar reorganization in people born without one hand raised a provocative suggestion that even the early sensorimotor cortex may also be function-specific rather than body-part specific (Hahamy et al., 2017). In contrast, our findings of no foot selectivity even in the complete absence of hands and in individuals who show strong compensatory strategies with foot use, point to limitations of the function-specific model with regard to the primary sensorimotor cortex.

The case of the hand primary sensorimotor cortex in dysplasics differs in several respects from the findings in the blind and deaf. Beyond the different sensory modality, these cases represent different stations of the cortical processing hierarchy. Specifically, in the blind and deaf, claims of functionally-selective organization are limited to the associative sensory cortices, whereas plasticity in people born without hands was tested

for the primary sensory-motor cortex. Therefore, while it may be that such principles could govern the organization of higher sensorimotor cortices, they do not seem to apply to the first cortical station processing touch, which is governed by topographic mapping of the body.

An additional difference between these cases is the extent of the deprivation of the sensory modality. In complete blindness or deafness there are no competing inputs within the sensory modality into the early sensory cortices, which could take over deprived parts of the topographic organization. Therefore, while the functional role of these regions is still debated (Amedi et al., 2017; Bedny, 2017; Campus et al., 2017), the topographic organization in the early stations of the hierarchy are retained (Striem-Amit et al., 2016; Striem-Amit et al., 2015). In higher stations of the cortical processing, the visual and auditory cortices also receive inputs from other modalities and from downstream cortical stations via feedback connectivity, which become more dominant in the complete absence of visual input. These may then drive cortex organization towards similar functions and domains even in the absence of the typical visual features driving this region. However, the case of an absence of one body part leaves intact inputs from proximal body parts in the topographic organization, generating within-modality competition and overtake. Inputs from nearby cortical stations or competing intra-modal inputs which would typically during development encourage differential specialization, sharpening cortical preferences (Foeller and Feldman, 2004), now drive the developing cortex more strongly than inputs from other functionally significant downstream stations which can direct it towards compensatory roles. The strongest input to the hand area territory would naturally come from its cortical neighbors, which are connected through horizontal direct and indirect (trans-synaptic) connectivity (Schieber, 2001). Indeed, the hand area of control subjects is also significantly activated as they move their shoulder (**Fig. 2C**), demonstrating the large extent of activity from the movement of one body part, and the overlap of body part representations in the primary sensorimotor cortex (Sanes and Donoghue, 2000; Schieber, 2001). The ability to evoke plasticity and takeover by nearby body parts has been confirmed in multiple studies of the effects of adult-stage amputation or deafferentation (Flor et al., 1995; Hall et al., 1990; Pons et al., 1991; Ramachandran et al., 1992; Sanes and Donoghue, 2000). It follows naturally that the same level of plasticity would be possible in earlier development, and in the case of congenital limb absence.

Importantly, competing inputs from much more remote locations such as the foot region may have limited (if at all) efficient connectivity to the hand area. During development, while the somatotopic maps are still being refined and pruned based on activity patterns and use (Foeller and Feldman, 2004; Martin et al., 2007), the extent of the maximal horizontal activation is already defined. This existing connectivity poses a constraint to potential plasticity and competing inputs over an area even in the case of completely missing body parts and their typical inputs. Thus, the current study reveals clear limitations for brain compensatory plasticity and for the role of experience in modifying brain organization.

Methods and materials

Participants: Five individuals born with severely shortened or completely absent upper limbs (individuals with upper limb dysplasia; dysplasics 1-5), and eight typically developed control subjects, matched for age (no group difference; $p < 0.25$) participated in the experiment. The causes of dysplasia were genetic, ototoxic medications (thalidomide) or unknown. See **Table 1** for the summary of the characteristics of the dysplasics, as well as images of their residual limbs. None of the dysplasics had a history of phantom limb sensations or movements, and all were adept at performing everyday actions and tool-use with their feet (see **Table S1** for a list of tools used with the feet). All the dysplasic participants were right-footed, and used their right foot dominantly. Dysplasic Subject D1 had three residual fingers attached to the shoulder (see **Table 1**). Dysplasic Subjects D2 and D3 had bilateral dysplasic malformations with totally missing upper limbs on both sides (a complete absence of arm, forearm, hand and fingers). Dysplasic Subject D4 had a shortened right arm (± 10 cm humerus). Dysplasic Subject D5 had one residual finger attached to the shoulder. The dysplasic individuals D1, D2, D4 and D5, apart from the congenitally missing hands, had a typically developed body. D3 had a shorter right leg (functionally corrected using a below knee leg and foot prosthesis). All participants

had no history of psychiatric or neurological disorder, and gave written informed consent in accordance with the institutional review board of Harvard University.

Dysplasic Subjects D1 and D3 report no history of prosthesis use. D2 occasionally used a wood composite prosthesis with locking elbow and hooks controlled by cables attached to leg straps from 3 to 7 years old, a wood composite prosthesis with electronic elbow and three pronged hooks controlled by micro switches in shoulder harness from 7 to 11 years old and a composite prosthesis with myoelectric elbows and cosmetic hands from 11 to 15 years old. D4 used switch-based right and left arms prostheses as a child and still uses occasionally a switch-based right arm prosthesis as an adult. D5 used myoelectric and manual prostheses five hours a day between 3 and 14 years old. All the subjects who have used prostheses report having used these prostheses mainly, if not uniquely, to pull, maintain in place or push objects but not to manipulate, and used objects for their functional use (e.g., eating with a fork) with their feet.

Experimental design: The motor experiment was carried out in a block design fMRI experiment (see acquisition detail below). Mouth, abdomen and either side hands (for the control subjects), shoulders and feet were moved (simple flexing movement) in separate blocks (6 s movement and 6 s rest) in randomized order according to an auditory cue (metronome). Flexing of the hands and feet entailed movements of closing of the palm (drawing the fingers together), flexing of the shoulder lifts it slightly, flexing of the abdomen tightens it, and flexing of the lips pursed the lips together. Four flex and relax movements were performed in each block at a frequency of 0.66 Hz. Due to our focus on the compensatory use of the feet, and as all the dysplasic participants were dominantly right-footed, we used the movements of the right hand and foot for further examination.

Functional Imaging: The BOLD fMRI measurements were obtained in a Siemens Tim Trio 3-T scanner at the Center for Brain Science at Harvard University and a 6-channel birdcage head coil. Functional images were acquired with a T2*-weighted gradient echo EPI (GE-EPI) sequence that employed multiband RF pulses and Simultaneous Multi-Slice (SMS) acquisition (factor of 3) (Moeller et al., 2010; Setsompop et al., 2012). The SMS-EPI acquisitions used a modified version of the Siemens WIP 770A. We used 69 slices of 2mm thickness. The data in-plane matrix size was 108x108, field of view (FOV) 21.6cm x 21.6cm, time to repetition (TR) = 2000ms, flip angle = 80˚ and time to echo (TE) = 28ms.
The main experiment had three runs of 186 whole-brain images each collected in one functional scan. The first two images of each scan (during the first baseline rest condition) were excluded from the analysis because of non-steady state magnetization.

Separate 3D recordings were used for co-registration and surface reconstruction. 3D anatomical volumes were collected using T1-weighted images using a MPRAGE T1-weighted sequence. Typical parameters were: FOV= 25.6cm X 25.6cm, data matrix: 256x256x256 (1mm iso voxel), TR=2530ms, TE=1.64, 3.5, 5.36, 7.22ms, flip angle = 7°.

Data analysis was performed using the Brain Voyager QX 2.8 software package (Brain Innovation, Maastricht, Netherlands) using standard preprocessing procedures. Functional MRI data preprocessing included head motion correction, slice scan time correction and high-pass filtering (cutoff frequency: 3 cycles/scan) using temporal smoothing in the frequency domain to remove drifts and to improve the signal to noise ratio. No data included in the study showed translational motion exceeding 2 mm in any given axis, or had spike-like motion of more than 1 mm in any direction. Functional and anatomical datasets for each subject were aligned and fit to standardized Talairach space (Talairach and Tournoux, 1988).

Anatomical cortical reconstruction procedures included the segmentation of the white matter using a grow-region function embedded in Brain Voyager. The Talairach normalized cortical surface was then used for surface-based alignment conducted across the subjects according to their cortical curvature (sulci and gyri) patterns. All further analyses were conducted in cortical space. Single subject data were spatially smoothed with a two dimetional 4 vertex full-width at half- maximum Gaussian in order to reduce inter-subject anatomical variability. Due to the small sample size of the unique dysplasic group, analyses were based on single subject (**Figs. S1, 2**) and probabilistic mapping of the overlap of significant single-subject activation (each at $p < 0.001$ uncorrected; **Figs. 1A, B, 2D**), to enable an assessment of the consistency of the findings. The hand sensorimotor cortex (delineated in white in **Figs. 1, 2**) was defined according to a full

overlap (100%) of activation to right hand flexing across all control subjects (each at $p < 0.001$ uncorrected). This region was further used to sample movement responses in each group (**Fig. 2C**) and as a seed to compute functional connectivity (**Fig. 2G, H, I**; see detail below). The contrast of foot selectivity vs. abdomen in the individual dysplasic subjects (**Fig. S3**) is depicted at a threshold of $p < 0.05$ uncorrected, to demonstrate that even at such lenient thresholds no foot selectivity is found at the lateral primary sensorimotor cortex.

Somatotopic preferential mapping was computed at a surface level for each dysplasic subject (**Fig. S2**). Each cortical vertex is colored based on the body part whose movement elicited the higherst activation (beta value). For group level somatotopic preferential mapping, group-level activation maps (hierarchical random effects general linear model, RFX GLM; (Friston et al., 1999)) at a surface level were used for each group seperately (**Fig. 2A, B**).

Group comparisons were conducted using Bayesian analyses (Jeffreys, 1998; Rouder et al., 2009), appropriate for testing small samples of unique populations and patients. The Bayes Factor is the probability of the data under one hypothesis relative to the probability of the data given another (H1/H0; H0 signifying no group difference, H1 signifying a difference between the groups) and, therefore, allows evaluating the strength of the evidence in the data for both alternatives. The Bayes factor (BF10) was calculated by first computing a two-samples independent two-tailed t test between the groups on the effect in question (e.g. in **Fig. 1C**, on the activation for each body part movements). BFs were computed based on the resulting t values using the Matlab function t2smpf provided by Sam Schwarzkopf (www.sampendu.wordpress.com/bayes-factors; (Rouder et al., 2009)). Bayes factor of over 5 is considered substantial evidence and BF over 10 is considered strong evidence against the null hypothesis (Jeffreys, 1998), in our case suggesting a group difference. To account also for the direction of the group difference, we computed an additional measure, Crawford modified t test (Crawford and Garthwaite, 2007; Crawford and Howell, 1998). Individual maps of selectivity (for **Fig. 2F**) and connectivity from the hand sensorimotor cortex (for **Fig. 2I**) of each dysplasic subject were compared with the maps of the control subjects in a Crawford modified t-test (Crawford and Howell, 1998). A probabilistic mapping of the overlap of significant individual-subjects t test results was computed (**Fig. 2F, I**) to enable an assessment of the consistency of the findings, reflecting the percentage of subjects showing this pattern. The probabilistic mapping of the functional connectivity differences is presented such that at least three (of five) dysplasic subjects need to have a difference from the controls, at $P < 0.005$ uncorrected, for a voxel to be shown.

Functional connectivity data analysis and MRI acquisition: A dataset of spontaneous BOLD fluctuations for the investigation of intrinsic (rest state; (Biswal et al., 1995)) functional connectivity was collected while the subjects lay supine in the scanner without any external stimulation or task. The pulse sequence used was gradient-echo EPI with parallel imaging (factor of 4). The data in-plane matrix size was 108x108, field of view (FOV) 21.6cm x 21.6cm, time to repetition (TR) = 1500ms, flip angle = 75˚ and time to echo (TE) = 28ms. 68 slices of 2mm thickness (with 0.2mm spacing) were used to obtain full coverage of the subjects' brain, and 400 whole-brain images were collected in one functional scan. The first two images of each scan were excluded from the analysis because of non-steady state magnetization. Ventricles and white matter signal were sampled using a grow-region function embedded in the Brain Voyager from a seed in each individual brain. Using MATLAB (MathWorks, Natick, MA) ventricle and white matter time-courses were regressed out of the data and the resulting time course was filtered to the frequency band-width of 0.1-0.01 Hz (in which typical spontaneous BOLD fluctuations occur). The resulting data were then imported back onto Brain Voyager for further analyses. Single subject data were registered to cortical space (as was done with the task data), and were spatially smoothed with a two-dimensional 4 vertex half-width Gaussian. The seed regions-of-interest (ROI) was defined for the sensorimotor hand region (100% overlap of controls individual activation for hand movement, $p < 0.001$ each). Individual time courses from this seed ROI were sampled from each of the participants, z-normalized and used as individual predictors in single-subject GLM analyses. For each group, functional connectivity parameter estimate values were sampled from regions showing full overlap probability of individual subjects' activation for each other body part (right foot, abdomen right shoulder and mouth), and averaged by group (**Fig. 2G**). for group comparison of FC patterns,

Bayesian statistics and the Crawford modified t-test were used as in for task activation comparisons. The Bayes factor (BF_{10}) was calculated from computing a two-samples independent t-test between the groups on FC to the hand area.

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Figures and Tables

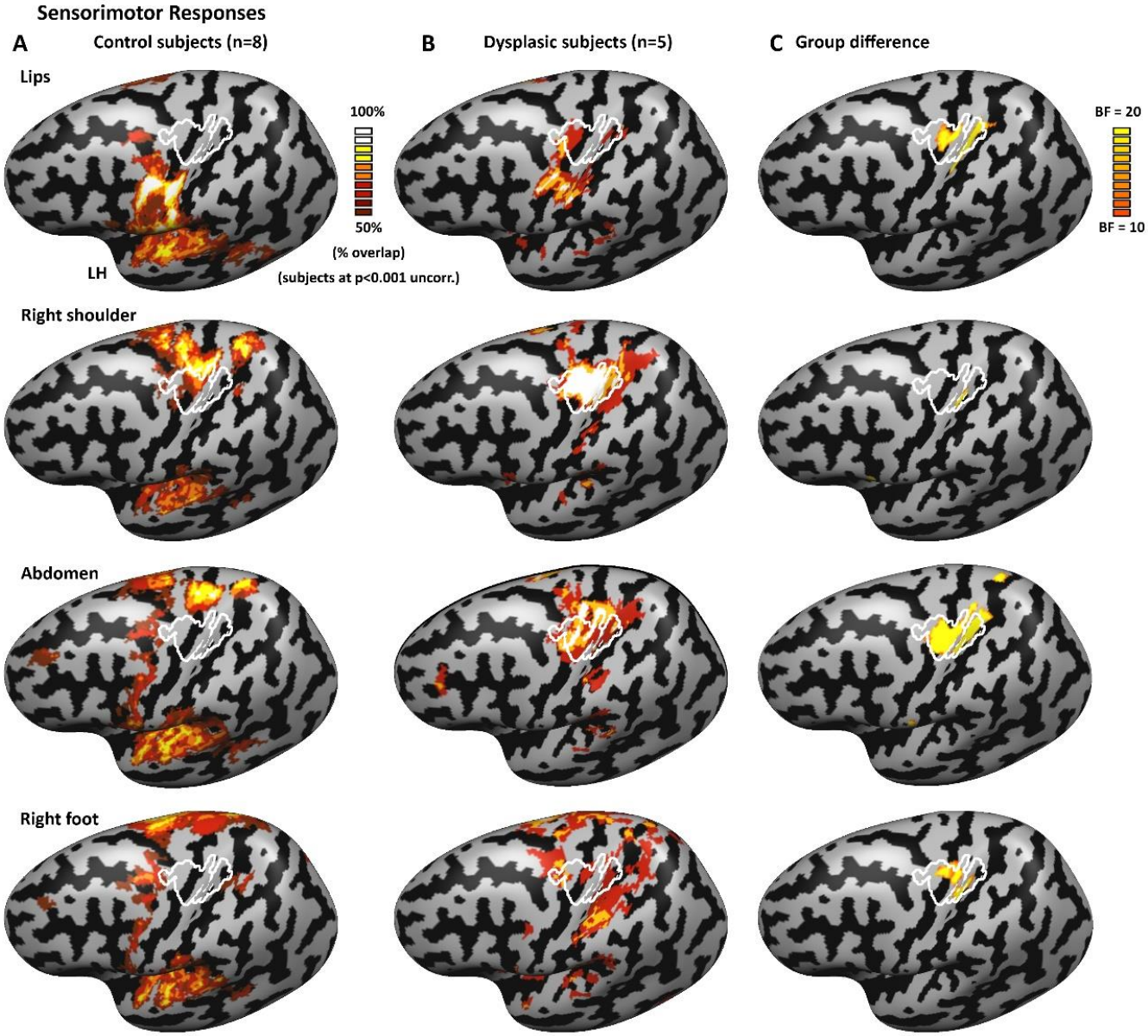


Figure 1: Activation for multiple body parts in the sensorimotor hand area in dysplasic subjects (born without hands)

A. Activation for body part movement (contraction of the lips, right shoulder, abdomen and right foot) in typically developed control subjects is shown on the left cortical hemisphere. The figure depicts a probabilistic mapping of the activation maps of individual subjects (each at $p < 0.001$ uncorrected), reflecting the percentage of subjects showing activation in each voxel. The activation patterns follow the standard Penfield homunculus. The sensorimotor hand area, delineated in white, represents the area activated by right hand movement in all (100%) of the control participants.

B. Probabilistic mapping of the activation for body part movement is shown for the dysplasic individuals, born without hands (see **Table 1**). Movement of each of the tested body parts elicited activation in the hand area to some extent, including, as previously reported, movement of the right foot.

C. Bayes factor (BF_{10}) for difference between the groups in their activation to body part movement is shown. The sensorimotor hand area is activated more by the dysplasic group for multiple body parts. $BF > 10$ represents strong evidence for the existence of a group difference.

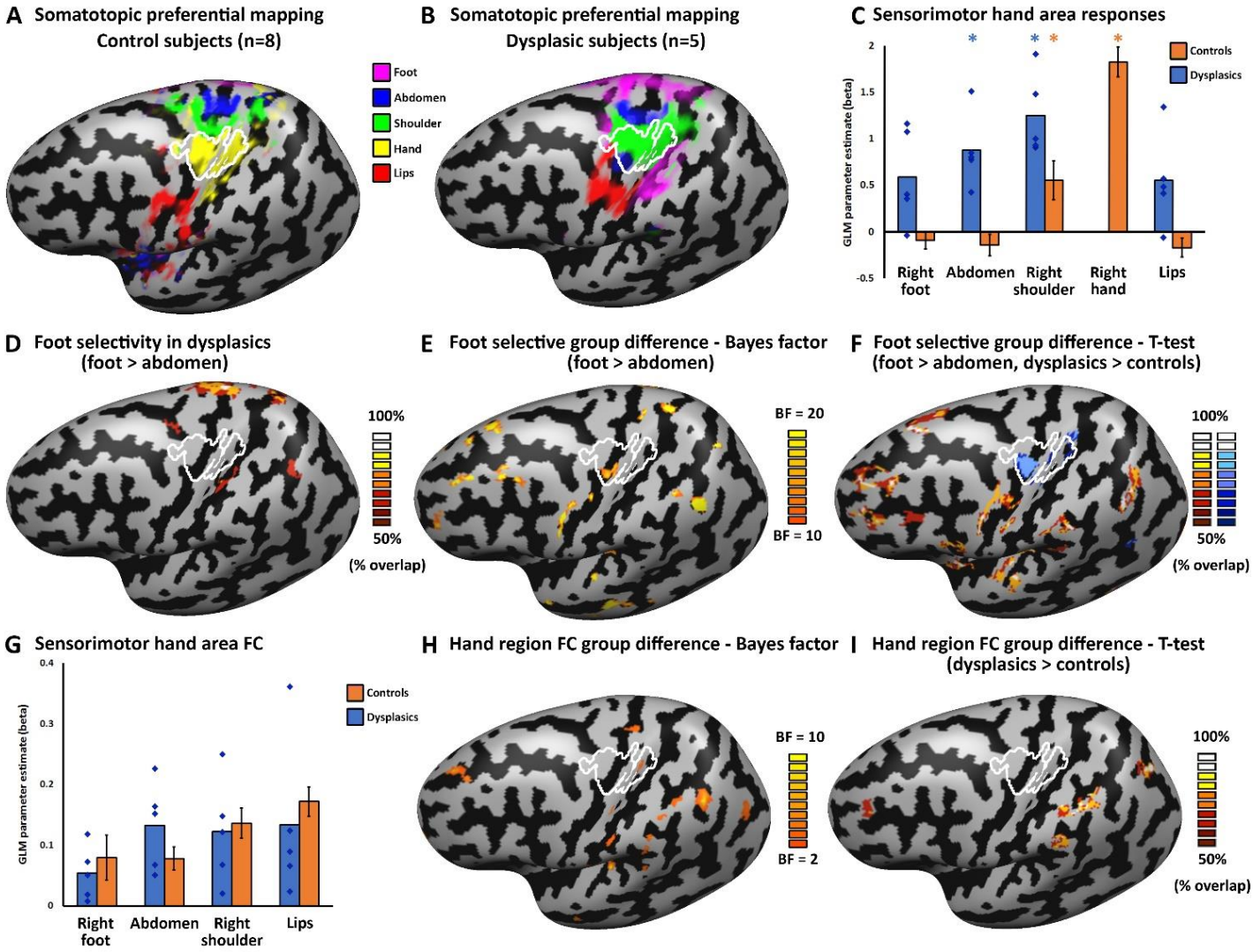


Figure 2: The sensorimotor hand area in the dysplasics does not show selectivity for the compensatorily used foot

A. Preferred body part responses for flexing movements (winner-takes-all approach) for the control subjects follows the standard Penfield homunculus.

B. Preferred body part responses for flexing movements for the dysplasic group shows a preference for shoulder (and to some extent abdomen) movements in the hand area, despite the extensive use of the feet to perform typically manual fine-motor tasks. For individual subject maps showing the reproducibility of this effect see **Fig. S2**.

C. Sensorimotor responses were sampled from the hand area, showing that this region in the dysplasics is more activated by proximal and lower body parts (shoulder and abdomen) than by foot movements. Error bars for the control group (orange bars) represent standard error of the mean. Individual data points (blue diamonds) are presented for the five dysplasic individuals in addition to the group average. Asterisks denote significant activation for each group vs. baseline ($p < 0.05$).

D. Foot movement selectivity (over abdomen movement) in the dysplasics can be found in the superior parietal lobule and premotor cortex, but not in the hand primary sensorimotor cortex. For individual subject maps see **Fig. S3**.

E. Bayes factor (BF_{10}) for difference between the groups in their differential activation to right foot movement (vs. abdomen movement) is shown. The dysplasics show different activation strength for right foot movement than the controls in various cortical loci, including the sensorimotor hand area.

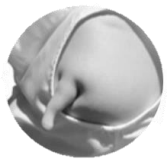
F. A direct comparison of the differential activation to right foot movement (vs. abdomen movement) between the dysplasics and control subjects was computed by Bayesian standardized difference test comparison of each dysplasic subject to the control group. The figure denotes a probabilistic mapping of differences, such that at least three dysplasic subjects would have to show a difference from the control subjects for a voxel to be marked. The sensorimotor cortex group difference seen in **Fig. 2E** appears to reflect less selective foot activation in the dysplasics as compared to the controls.

G. Functional connectivity between the sensorimotor hand area and sensorimotor areas for the right foot, abdomen, right shoulder and mouth (defined per group) are shown for each group. The hand sensorimotor cortex of the dysplasics does not show increased functional connectivity to the foot area. Error bars for the control group represent standard error of the mean. Individual data points are presented for the five dysplasic individuals.

H. Bayes factor (BF_{10}) for difference between the groups in their functional connectivity from the sensorimotor hand area is shown, not revealing any increased connectivity to foot sensorimotor areas, or otherwise any strong connectivity differences between the groups. At a Bayes factor of over 5 (considered substantial evidence against the null hypothesis of no group difference), only a small cluster at the inferior parietal lobule shows a group difference in FC.

I. A direct comparison of functional connectivity from the sensorimotor hand area between the dysplasics and control subjects was computed by Bayesian standardized difference test comparison of each dysplasic subject to the control group. The figure denotes a probabilistic mapping of differences, such that at least three dysplasic subjects would have to show a difference from the control subjects for a voxel to be marked. Again, no consistent significant difference is evident in the sensorimotor cortex.

Table 1: Characteristics of the dysplasic subjects

Subject ID	Age	Gender	Causes of dysplasia	Hand Prosthesis use	Years of education	Upper limb structure
D1	21	F	Unknown	None	15	
D2	54	M	Thalidomide	Past use of functional and cosmetic prostheses (see methods)	12	Completely missing upper limbs bilaterally
D3	27	F	Unknown	None	15	Completely missing upper limbs bilaterally
D4	37	M	Unknown	Past and current occasional use of functional prostheses	17	Completely missing upper limb on the other side 
D5	31	F	Genetic	Past use of functional prostheses	15	Completely missing upper limb on the other side 

Supplementary material

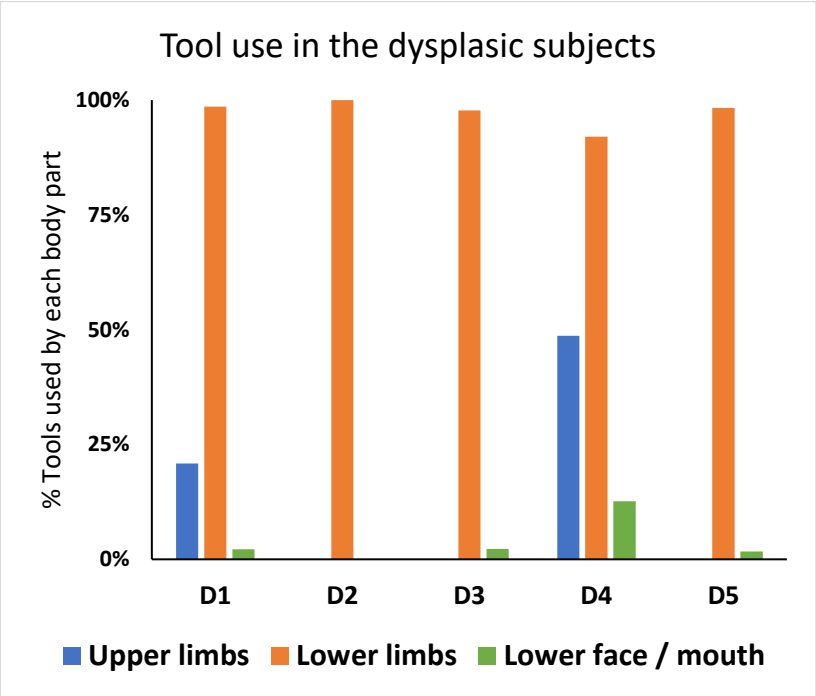


Figure S1: Everyday tool use by the dysplasic subjects

The dysplasics were provided, over a month before the scan, with a list of 187 tools and small graspable objects and noted for each which body part they use if with (upper limbs, lower limbs, mouth, multiple items can be marked for the same item) or if they have never used it before to achieve its typical function. The figure depicts the percentage of using each body part, for the items they reported to have used before, for each dysplasic individual. All the dysplasic subjects reported to use tools with their lower limbs for the clear majority of tools they have experienced using. Foot tool-use accounted for a minimum of 92% of the used tools, although some tools were jointly manipulated by the lower face or remaining upper limbs in specific individuals (in subjects D1 and D4).

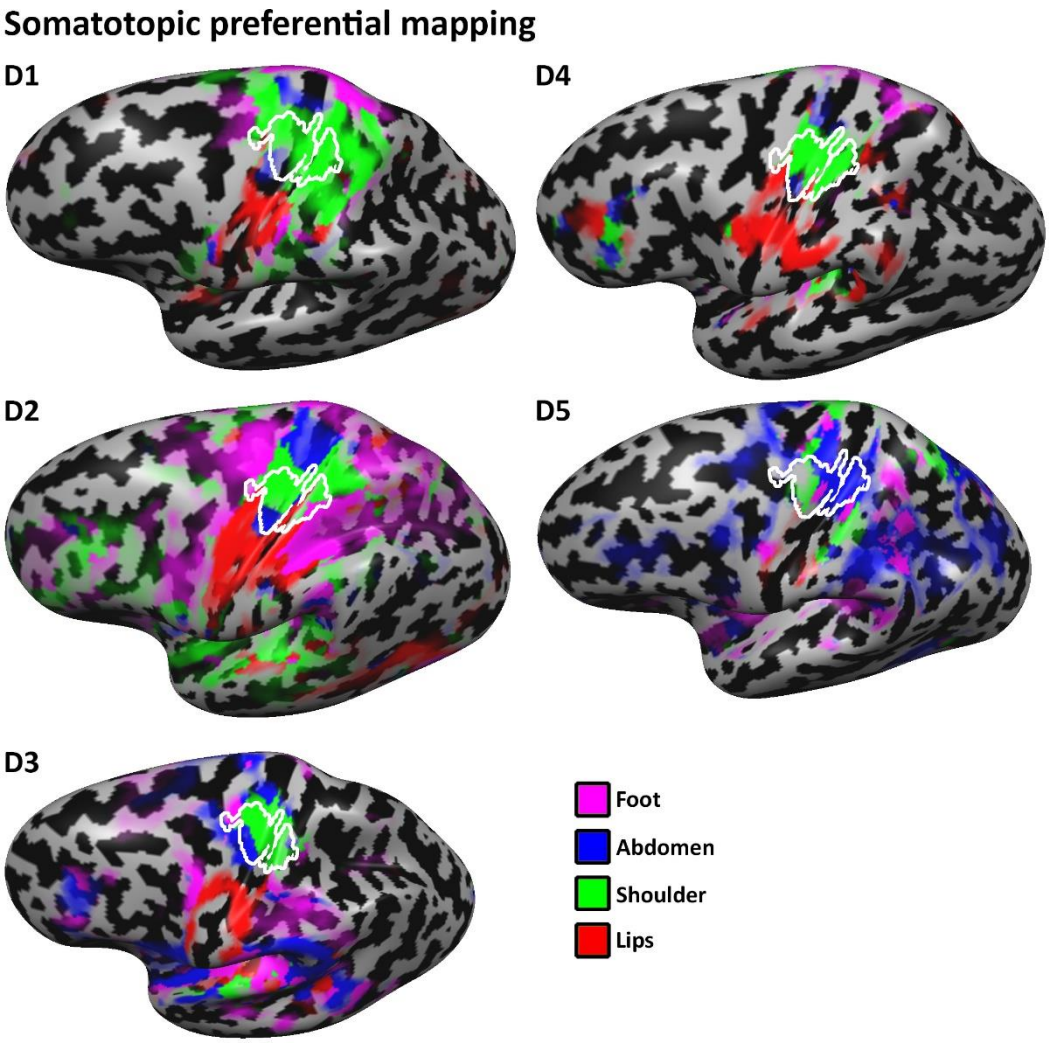


Figure S2: Somatotopic mapping in individual dysplasic subjects

Preferred body part responses for flexing movements for the dysplasic individuals largely replicates the group patterns (**Fig. 2B**), showing a preference of the lateral sensorimotor cortex (the hand area is delineated in white) to movements of the shoulder and abdomen and not of the foot, despite the extensive use of the feet to perform typically manual fine-motor tasks. The sensorimotor hand area, delineated in white, represents the area activated by right hand movement in all (100%) of the control participants, aligned to the dysplasics cortices according to the pattern of cortical folding.

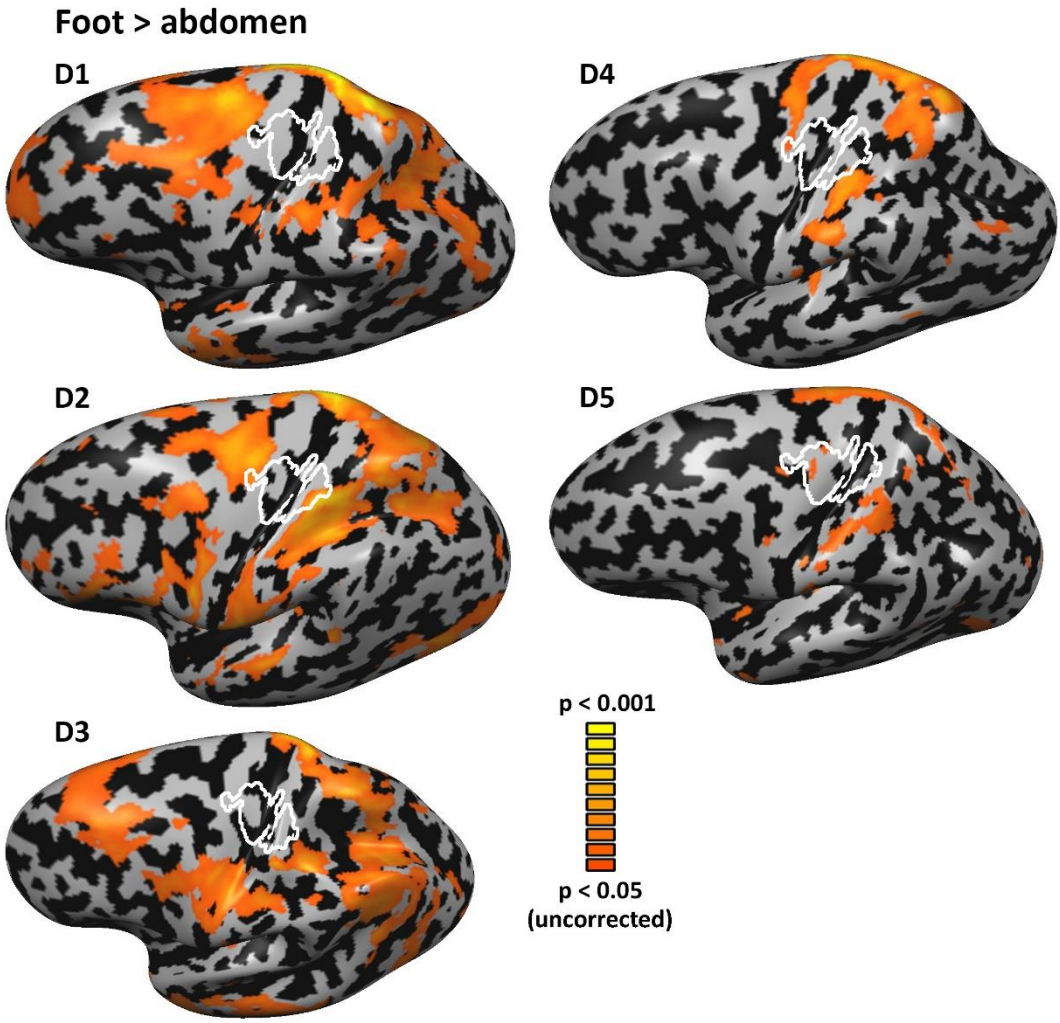


Figure S3: Selective foot activation in the dysplasic individuals

Foot movement selectivity (over abdomen movement) in the dysplasic individuals can be found among other areas in the superior parietal lobule and premotor cortex, but almost nowhere (apart from small cluster in subject D5) in the hand primary sensorimotor cortex (delineated in white), despite the use of a lenient threshold of $p < 0.05$ uncorrected. No activation in the primary sensorimotor hand area in any of the dysplasic subjects is found when correcting the data for multiple comparisons. The sensorimotor hand area, delineated in white, represents the area activated by right hand movement in all (100%) of the control participants, aligned to the dysplasics cortices according to the pattern of cortical folding.

Table S1: List of tools all five dysplasic subjects reported to have already used to achieve their typical function with their lower limbs, and with them only*.

Bowl scraper	Cooking strainer	Glue stick	Kitchen sponge	Razor	Syringe
Calculator	Correction pen	Hair brush	Match	Rolling pin	Tambourine
Can opener	Elastic band	Hairdryer	Nail	Scissors	Thermometer
Cards	Erasing gum	Hand fan	Nail polish	Screw	Toaster
Chess pawn	File	Hole punch	Paper clip	Sewing needle	Toothbrush
Comb	Frisbee	Iron	Pencil sharpener	Spinning top	Vegetable peeler
Computer mouse	Garlic press	Kettle	Protractor	Stapler	Yo-yo

*The instruction the dysplasic subjects were given was the following:
Please indicate your experience in using the listed objects by putting X in the appropriate column (columns were “I use it with my upper limb(s)”; “I use it with my lower limb(s)”; “I use it with my mouth”; “I have never used it to achieve its typical function”; “I would be able to use it to achieve its typical function, if I had the opportunity to try”; “?”.). If you have already used the object to achieve its typical function (e.g., using a hammer to put on a nail, using a sword to sword fight and so on), please indicate whether you used your upper limbs, lower limbs or mouth to use it. If you use an object with a combination of several body parts or if you use indifferently different body parts to use it, please put X in all the appropriate columns (for instance lower limbs and mouth). If you have never used a given tool to achieve its typical function, that is, if you have never touched it or if you have only transported it, then put X in the column “I have never used it to achieve its typical function” and, then, indicate whether you estimate that you would nevertheless be able to use it to achieve its typical function if you were given the opportunity by putting a X in the last column, or not, by letting the last column empty. If you don’t know the object, or if you are not sure of what it refers to, or if you are not sure of your response, put a X in the column “?”.