

Sensorimotor-independent development of hands and tools selectivity in the visual cortex

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The visual occipito-temporal cortex is composed of several distinct regions specialized in the identification of different object kinds such as tools and bodies. Its organization appears to reflect not only the visual characteristics of the inputs but also the behavior that can be achieved with them. For example, there are spatially overlapping responses for viewing hands and tools, which is likely due to their common role in object-directed actions. How dependent is occipito-temporal cortex organization on object manipulation and motor experience? To investigate this question, we studied five individuals born without hands (individuals with upper limb dysplasia), who use tools with their feet. Using fMRI, we found the typical selective hand-tool overlap (HTO) not only in typically developed control participants but also in four of the five dysplasias. Functional connectivity of the HTO in the dysplasias also showed a largely similar pattern as in the controls. The preservation of functional organization in the dysplasias suggests that occipito-temporal cortex specialization is driven largely by inherited connectivity constraints that do not require sensorimotor experience. These findings complement discoveries of intact functional organization of the occipito-temporal cortex in people born blind, supporting an organization largely independent of any one specific sensory or motor experience.

body image | brain development | motor deprivation | tool use | visual cortex

The visual occipito-temporal cortex contains multiple domain-sensitive regions (1) that are highly reproducible across individuals. Much is known about these regions' large-scale organization. Consistent with the patterns of neuropsychological dissociations showing a fundamental distinction between animate and inanimate objects (2, 3), neuroimaging results have shown that the animate/inanimate distinction is the primary organizational dimension in the occipito-temporal cortex (4–8), with a secondary distinction within the inanimate domain between navigation-relevant (e.g., large nonmanipulable objects and scenes) and small, manipulable inanimate objects (9–12). What are the principles that guide this organization? One possibility is that it is the direct result of experience, critically dependent on the individual's life experiences and expertise (13–17). An alternative is that experience merely modulates an already existing innately determined structure, driven by connectivity constraints (4, 18–21) between regions within the occipito-temporal cortex and downstream areas specialized in processing specific object types.

A notable example supporting the close link between visual form processing and its downstream use is a specific region in the occipito-temporal cortex that shows spatially overlapping preferences for hands and tools (22, 23). This overlapping specialization is obviously not based on visual similarity alone because hands and tools are visually quite distinct. Nor is it due to general domain specialization because animate and inanimate objects are otherwise distinct (24–26). Instead, the overlap may reflect the importance of processing their shapes concomitantly during tool manipulation, and the extent to which the objects extend the body effectors (23). Furthermore, this region of the occipito-temporal cortex belongs to a functional network encompassing sensorimotor and fronto-parietal regions implicated in tool manipulation

and action (27, 28), again stressing the link between the occipito-temporal cortex and object manipulation.

What drives this specialization? And what is the role of experience in shaping visual cortex organization? There is evidence that visual experience is not necessary for developing object preferences in the occipito-temporal cortex. The visual cortex of congenitally blind individuals shows the typical organization of object domain selectivity (18, 20, 29–31), including for body shapes and tools (32, 33). Although the preserved specialization for body shapes and tools does not depend on visual experience this does not mean that it does not require other sensorimotor experience for its emergence. Thus, for example, it is not unreasonable to assume that specialization for body shapes and tools in visual cortex may depend on such sensorimotor experience as palpating and using tools with the hands. The alternative hypothesis is that domain-specific specialization is innately determined and does not depend on any specific (ontogenetic) sensorimotor experience for its emergence.

Here, we ask whether this organization is critically dependent on sensorimotor experience. We do this by studying whether a similar domain overlap, between hands and tools, is found in individuals born without hands (individuals with upper limb dysplasia), who have no hand motor experience, and instead use tools with their feet.

Results

We studied a group of five people born with severely shortened or completely absent arms and no functional hands (dysplasias) (Table S1) and a group of typically developed controls to assess the role of sensorimotor experience in driving the visual cortex overlap between the hand and tool regions.

Significance

To what extent is brain organization driven by innate genetic constraints, and how dependent is it on individual experience during early development? We show that an area of the visual system that processes both hands and tools can develop without sensorimotor experience in manipulating tools with one's hands. People born without hands show typical hand-tool conjoined activity, in a region connected to the action network. Taken with findings from studies with people born blind, who also show intact hand and tool specialization in the visual system, these findings suggest that no specific sensory or motor experience is crucial for domain-specific organization of visual cortex. Instead, the results suggest that functional brain organization is largely innately determined.

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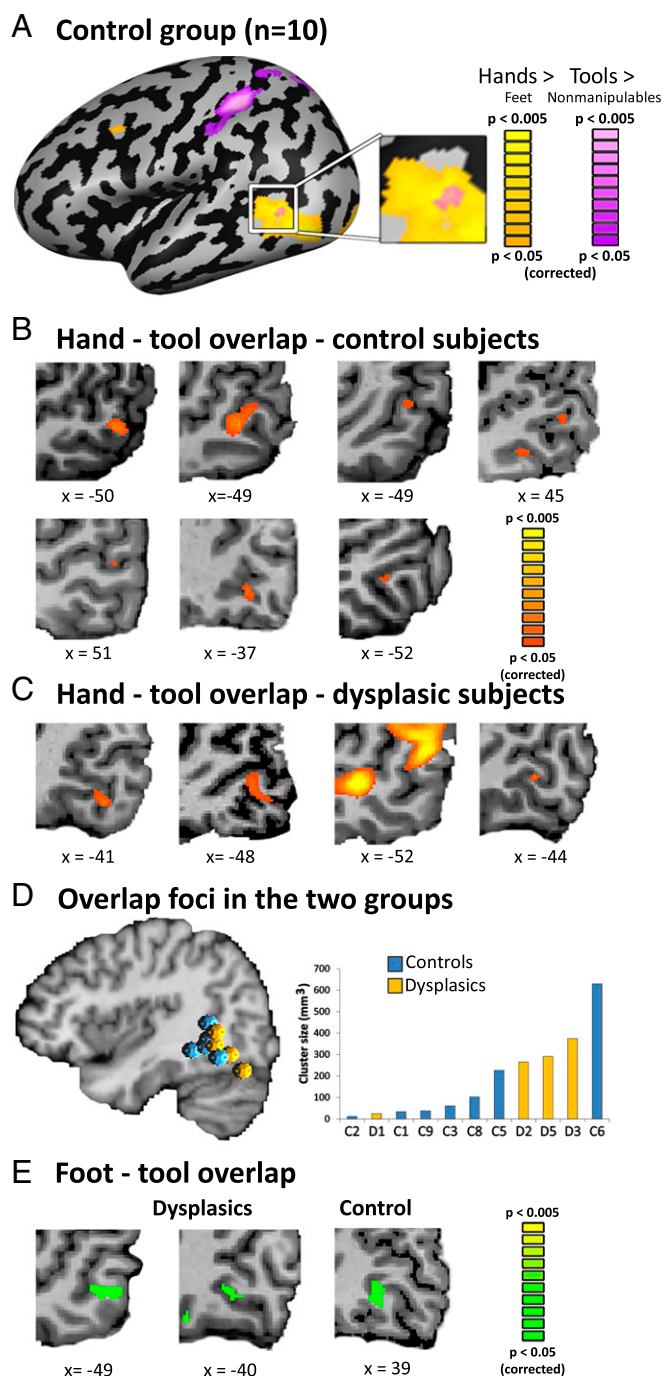


Fig. 1. Hand-tool visual cortex overlap does not require hands. (A) The hand and tool selectivity overlap (HTO) in the lateral occipito-temporal cortex is replicated in typically developed control subjects ($n = 10$, RFX GLM, $P < 0.05$, corrected for multiple comparisons). Yellow marks hand selectivity over feet, and purple marks tool selectivity over nonmanipulable artifacts. (B) The HTO, in the occipito-temporal cortex, can be found at the individual level in the majority (7 of 10) of the controls (for cortical surface views, see Fig. S2). (C) A majority of the dysplasics (4 of 5) born without hands show an overlap between hand and tool selectivity in the visual cortex. This suggests that motor experience is not critical for the formation and specialization of the visual-cortex hand action-related representations. (D) The location (Left; spheres denote the location of individual subjects HTO peaks) and size (Right) of the HTO in the dysplasics (marked yellow) did not differ from that of the control subjects (marked blue). (E) In addition to the overlap between hand and tool selectivity, 2 of the dysplasics (2 of 5) and 1 of the controls (1 of 10) show an overlap of feet and tools selectivity [a foot-tool overlap (FTO)]. This potentially suggests visual cortex

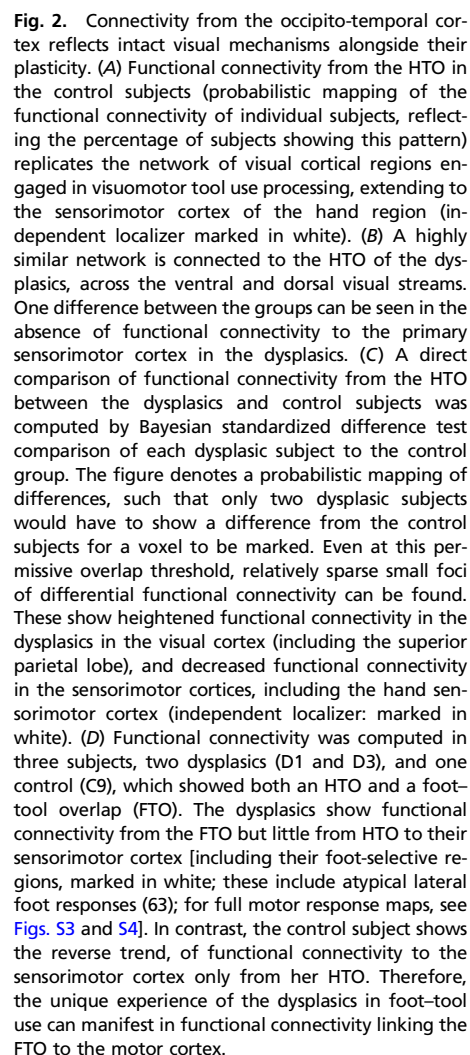
We first applied a strict contrast of hand selectivity (vs. viewing images of feet) and tool selectivity (vs. nonmanipulable artifacts), and replicated, in the control group, the established overlap between the regions in the occipito-temporal cortex (Fig. 1A). In individual participant analyses, 7 out of the 10 control participants showed this overlap (Fig. 1B), in agreement with previous findings (22), although two of them showed this overlap in the right rather than the left hemisphere (see Table S2 for Talairach coordinates of the individual peaks). Importantly, among the dysplasics, four of the five participants also showed this overlap (Fig. 1C; dysplastic subjects 1, 2, 3, and 5). The hand-tool overlap (HTO) area shows a clear preference for viewing hands—it is spatially distinct from an area showing preference for viewing feet, and it is anterior to motion-selective regions (Figs. S1 and S2). Furthermore, its activity patterns for hands and feet are reliably distinguishable, for both dysplastic and control subjects: the activity patterns were statistically different in all but one control subject when classifying hand and foot responses using a multivariate pattern analysis (MVPA) approach within each subject's HTO (average classification accuracy of 72.5% in the dysplastic subjects and 70.7% in the control subjects; $P < 0.05$).

Neither the location nor the size of the HTO was statistically different between the groups (see Fig. 1D for the overlap loci and size distribution), as assessed by Bayesian analysis. Bayes factor (BF) was below 1 (BF = 0.76 for HTO location and BF = 0.55 for HTO size), favoring the absence of difference between the groups. Therefore, the typical HTO development does not require manual motor experience.

What drives the emergence of the HTO in the dysplasics? One explanation of domain-specific specialization in visual cortex is based on the observation that objects differ in the kinds of computations necessary for their recognition and their use, and that the different computations recruit distinct brain regions. For example, the grasping response for using a hammer involves different neural regions than those engaged in the navigation of a visual scene among large nonmanipulable objects, implying the recruitment of distinct neural circuits for their effective processing (34). A possible implication of this fact is that visual regions become specialized for processing specific visual properties in part because of their connectivity with relevant downstream regions. Additionally, to the extent that object domains typically share visual characteristics that distinguish them from other object domains (35–37), this would result in domain-specific visual regions that are associated with distinct neural circuits (4, 18).

Can the same connectivity pattern blueprint exist in the dysplasics, despite the absence of hands? Or do different mechanisms and different connectivity patterns (unrelated to dorsal stream and action networks) explain the same finding in this case? To address these questions, we computed the functional connectivity from each control subject's individual HTO peak in an independent resting-state measurement. Group analysis of the connectivity patterns replicate the results from previous studies (22, 27): We found that the HTO is significantly functionally connected to vast regions in the visual system (Fig. 2A), both in the ventral and dorsal stream, extending as far as the primary sensorimotor cortex, specifically its hand region (Fig. 2A, independent functional motor localizer marked in white). Computing the functional connectivity from HTO in the dysplasics shows a very similar pattern (Fig. 2B), connecting the HTO to widespread areas in the parietal lobe. The connectivity pattern is largely retained, such that a permissive comparison of the groups [Bayesian standardized difference test comparison of each dysplastic subject to the control group (38) and probabilistic mapping of differences in as little as two subjects; see *Materials and Methods* for detail] shows only sparse small foci of

organization is also somewhat plastic to changes due to different individual sensorimotor experience.



In recent years, it has been found that viewing hands and tools recruits overlapping cortical areas in the occipito-temporal cortex. A fundamental question concerns the nature of the principles driving this topographical bias. One possible explanation is that the HTO emerges through repeated sensorimotor experience of using tools with the hands. Consistent with this view is the observation

that the HTO is located in a region of the occipito-temporal cortex showing preferential functional connectivity (22, 27) with the network of left-lateralized (40) areas of the dorsal visual stream and motor cortex involved in tool manipulation. These include the anterior intraparietal area [involved, among other tasks, in producing accurate grip (41–43)] and the ventral premotor cortex (44–46). Furthermore, the fact that similar tool-selective and body-selective responses have been found in the same part of the occipito-temporal cortex in individuals deprived of visual experience from birth (32, 33, 47, 48), invites the inference that, because vision is not necessary for developing these preferences, the burden for shaping this region's functional specialization is carried by motor experience. Our finding, however, calls for a reexamination of this experience-based account. We found that individuals born without hands who, therefore, have never grasped or manipulated tools with the hands, show the typical overlap between hands and tools selectivity in the occipito-temporal cortex, indistinguishable in volume or location from that of the controls. They also showed a largely similar functional connectivity of this region to the left intraparietal sulcus involved in tool use. This was found even in subjects who have never used prostheses (two dysplastic subjects) and in a subject who has only used functional (hook-like) prostheses, which cannot be used to manipulate tools (see detail in *Materials and Methods*). Therefore, these subjects had no experience in manipulating tools with instruments visually similar to hands. A clear example of the independence of HTO from manual motor experience is ID3, who has completely absent upper limbs, has no prostheses experience, and shows intact HTO (the largest overlap volume among the dysplasics) and functional connectivity (Fig. 2D). We can thus conclude that this specialization of the high-level visual cortex for hands and tools does not require manual tool use experience for its emergence.

If ontogenetic experience, be it visual or motor, is not the crucial force driving the topographical specialization for tools and hands in the occipito-temporal cortex, how can we explain that tools and hands processing overlaps in this brain region? Our results encourage the hypothesis that the organization of evolutionarily relevant object domains in high-level visual cortex is mainly driven by the differential connectivity of its different regions with different downstream networks in the service of behavior (4, 18). The hypothesis is that the brain could have evolved specialized representational systems in high-level visual cortex, which are particularly sensitive to object features that are strongly associated with different object domains. On this view, the HTO would have emerged because of the potential advantage that accrues from the efficient processing of hands and tools as parts of a common (or closely intertwined), specialized system. This system, in turn, is connected to the dorsal, action-processing areas to allow quick and efficient shaping of hands to grasp and use tools. Once evolved, this innately determined system would manifest itself ontogenetically even in the absence of any of the specific inputs, as in the case of the dysplasics, that originally contributed to the full usefulness of the pattern.

The results reported here and the results obtained with congenitally blind individuals (32, 33, 47) show that motor and visual experience are singly unnecessary for the full development of the hand and tool specialization in the occipito-temporal cortex. However, it is possible that visual experience (e.g., in the dysplasics) and motor experience (e.g., in the blind subjects) are each sufficient for the development of hand and tool specialization in the occipito-temporal cortex. Still, to account for the topographic arrangement of the hand and tool specialization, we would need to assume that the region in question is preferentially disposed to encode information about those object categories independently of a specific type of sensory input. This would, in turn, suggest that the nature of representations in this region would need to be of a form that is accessible through different modalities, including written words (48), haptic stimulation (49, 50), or sensory-substitution-based audition (51), and that they be independent from low-level effector-

bound motor properties and experience, such that they develop normally in individuals with atypical bodies, as in the dysplasics.

It is important to note that the view presented here does not preclude a role for sensorimotor experience in the fine details of the organization of the occipito-temporal cortex. In fact, a finding of this study—namely, that in addition to the HTO two dysplasics also displayed a conjoined foot and tool selectivity, functionally connected to the dorsal, action-processing areas and sensorimotor cortex—seems to encourage this possibility. Curiously, the two dysplasics who show this effect had never used prostheses. However, it is not easy to know how to best interpret this observation as not only these two dysplasics but also one typically developed participant showed a FTO (but dissimilar functional connectivity patterns). Although potentially indicative of some experience-based modulation of occipito-temporal cortex organization, current results do not allow clear conclusions about such modulation.

The results reported here have indirect but clear implications for claims regarding the role of motor simulation in action recognition. On such theories, recognition of a hand action is claimed to depend on the simulation of the viewed action in the observer's own motor system (52). Individuals born without upper limbs recognize hand actions without difficulty and show the same patterns of behavior as typically developed individuals in various hand movement and action recognition tasks, suggesting that motor simulation is not causally involved in action recognition (53). However, it has been proposed that, in the impossibility of hand motor simulation, a cross-limb matching of the viewed action in such individuals would be performed implicitly with the feet, based on experiencing their synchronous co-occurrence (54). However, the HTO of the dysplasics does not show functional connectivity to their sensorimotor foot region, which could have suggested the existence of such implicit imitation (Fig. 2B). Furthermore, in additional control experiments, no positive activation was found in the HTO of the dysplasics when performing unseen grasping or reaching movements with their feet ($\beta = 0.13$, $t = 1.79$, $P > 0.21$; see Fig. S4 and *Materials and Methods* for detail). This stands in contrast to finding motor responses for unseen hand (but not foot) movements in the controls' HTO (Fig. S4). Therefore, the current data do not support an alternative motor explanation for the existence of the HTO in the absence of hands and do not support the hypothesis that hand action perception involves motor simulation with the feet.

In conclusion, the clear preservation of functional organization of hand- and tool-sensitive regions in the occipito-temporal cortex in people born without hands suggests that sensorimotor ontogenetic experience is not required for the specialization of the occipito-temporal cortex. Instead, it points to an evolutionarily driven functional selectivity, which can develop based on inherited connectivity constraints (18).

Materials and Methods

Participants. Five individuals born with severely shortened or completely absent upper limbs (individuals with upper limb dysplasia; dysplasics 1–5), and 10 typically developed control subjects, matched for age (no group difference; $P < 0.29$), participated in the experiment. The causes of dysplasia were genetic, ototoxic medications (thalidomide), or unknown. See Table S1 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. Dysplastic subject D1 had three residual fingers attached to the shoulder (Table S1). Dysplastic subjects D2 and D3 had bilateral dysplastic malformations with totally missing upper limbs on both sides (a complete absence of arm, forearm, hand, and fingers). Dysplastic subject D4 had a shortened right arm (± 10 -cm humerus). Dysplastic subject D5 had one residual finger attached to the shoulder.

Dysplastic subjects D1 and D3 report no history of prostheses use. For full detail of participants D2, D4, and D5 prosthetic use see *SI Materials and Methods*. Importantly, the prostheses used by D4 and D5 did not include cosmetic hands and all of them report having used these prostheses mainly, if not uniquely, to pull, maintain in place, or push objects but not to manipulate and use objects for their functional use (e.g., eating with a fork) with their feet.

All participants had normal or corrected-to-normal vision, had no history of psychiatric or neurological disorder, and gave written informed consent in accordance with the institutional review board of Harvard University.

Experimental Design. Grayscale pictures depicting a hand, a foot, a tool, or a nonmanipulable artifact were displayed in a block design. All epochs lasted 8 s and were followed by an 8-s rest interval. Eight images of different objects from the same category were presented in each epoch; each image was presented for 800 ms and was followed by a 200-ms blank screen. A central red fixation point was presented throughout the experiment. The experiment had four runs, and each condition was repeated eight times in a pseudorandom order in each run. The subjects were instructed to fixate and respond (by foot response) to catch trials, in which an image was repeated twice consecutively. There were two catch trials in each run of the experiment, and the data from these trials were excluded from further analysis.

The tools and nonmanipulable artifacts categories included eight different objects, with 16 different exemplars each. The hands and legs included 16 different exemplars each. Objects were matched across categories for familiarity ($P < 0.82$) and differed significantly on manipulability (tools and nonmanipulable artifacts' manipulability average, 6.87 and 1.25, respectively; $P < 0.00001$) based on the ratings (scores of 1–7) of independent control groups using Amazon Mechanical Turk. Tools were chosen from a list of items that all dysplasics reported using with their feet (see *SI Materials and Methods, Stimuli* for the full list all dysplasics reported to have used with their feet).

For full detail of the ratings and other stimulus parameters, see *SI Materials and Methods*. Stimuli images were matched in number of pixels, vertical size, horizontal size, and vertical–horizontal ratio, to eliminate any low-level visual confound.

Functional Imaging. The blood oxygen level-dependent (BOLD) fMRI measurements were obtained in a Siemens Trio 3-T scanner at the Center for Brain Science at Harvard University. For acquisition detail, see *SI Materials and Methods*. The main experiment had four runs of 287 whole-brain images each collected in one functional scan. Data analysis was performed using the BrainVoyager QX 2.8 software package (Brain Innovation) using standard preprocessing procedures (see *SI Materials and Methods*). Functional and anatomical datasets for each subject were aligned and fit to standardized Talairach space (55). Single-subject data were spatially smoothed with a 3D 6-mm full-width at half-maximum Gaussian to reduce intersubject anatomical variability, and then grouped using a general linear model (GLM). Group analyses in the control group were conducted in a hierarchical random effects analysis (RFX) (56) at a surface representation level, due to the variability of the lateral occipito-temporal cortex location in volumetric space. Anatomical cortical reconstruction procedures included the segmentation of the white matter using a grow-region function embedded in BrainVoyager. The Talairach normalized cortical surface was then inflated, and the obtained activation maps were superimposed onto it. Surface-based alignment was conducted across the subjects according to their cortical curvature (sulci and gyri) patterns, and RFX GLM analysis (Fig. 1A) was then conducted.

Due to the small sample size of the unique dysplastic group, analyses were based on single subject (Fig. 1C and E) and probabilistic mapping of the overlap of significant single-subject activation (Fig. 2B), to enable an assessment of the consistency of the findings. The minimum significance level of the results presented in this study was set to $P < 0.05$, corrected for multiple comparisons, using the spatial extent method based on the theory of Gaussian random fields (57, 58) (a set-level statistical inference correction). Individual HTO activation (a conjunction of two conservative contrasts) was corrected for multiple comparisons using the spatial extent method within the visually active occipital and occipitotemporal cortex [all image types vs. baseline, in both groups, $P < 0.05$, false-discovery rate (FDR) (59) corrected]. This was done based on the Monte Carlo stimulation approach, extended to 3D datasets using the threshold size plug-in for BrainVoyager QX.

Comparison between the two groups in peak location of the HTO was applied using the BF approach (60), appropriate for testing small samples of unique populations and patients. The BF is the probability of the data under one hypothesis relative to the probability of the data given another (H0/H1)

and, therefore, allows evaluating the strength of the evidence for both alternatives. We calculated and compared the mean Euclidean distance between each of the dysplasics HTO peak and each of the controls (between-group distance, mean = 12.6 mm, SD = 6) and the mean distance of each of the controls to the other controls (within-group distance, mean = 9.7 mm, SD = 2.38). The BF for the comparison between the groups' average distance was calculated twice, once without the two control subjects whose HTO appeared in the right hemisphere (BF = 0.64, $P > 0.41$) and once when their peaks were included but reversed in laterality (BF = 0.76, $P > 0.25$). BF analysis was also used to compare HTO volume between the groups (BF = 0.56, $P > 0.53$). In all cases, BF was below 1, favoring the absence of difference between the groups.

MVPA was conducted in spheres centered at the individual HTO peaks (4-mm radius). MVPA was performed using a linear support vector machine classifier as implemented by BrainVoyager. Within each individual region of interest (ROI), z-normalized β weights were estimated based on eight trials per condition (hands, feet) and run, resulting in 32 β values per condition. Classification accuracies were computed using leave-five-out cross-validation, that is, the classifier was trained using the data of 27 patterns and tested on its accuracy at classifying the unseen data from the remaining 5 patterns. The average classification was tested against classification with a random permutation of trial labels (1,000 iterations), averaged across the cross-validation procedures.

Functional Localizers and Control Experiments. Functional localizers for sensorimotor cortex hand and foot regions, grasping control experiment, and a visual motion selectivity experiment were also conducted. For details, see *SI Materials and Methods*.

Functional Connectivity Data Analysis and MRI Acquisition. A dataset of spontaneous BOLD fluctuations for the investigation of intrinsic [rest state (61)] functional connectivity was collected while the subjects lay supine in the scanner without any external stimulation or task. A total of 400 whole-brain images was collected in one functional scan. For details of the acquisition and preprocessing parameters, see *SI Materials and Methods*. Single-subject data were spatially smoothed with a 3D 6-mm half-width Gaussian. Seed ROIs were defined as spheres (4-mm radius) around each subject's peak of hand–tool selectivity overlap in the occipito-temporal cortex (Fig. 1D), to avoid confounds related to seed size. 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. Probability overlap across the individual subjects (Fig. 2A and B) were computed from individual maps, each at $P < 0.05$, FDR corrected for multiple comparisons. The maps were overlaid, and the percentage of subjects showing activation at each voxel was calculated. Functional connectivity group comparison (Fig. 2C) was conducted using Bayesian standardized difference test appropriate for comparing a single case to a control/normative sample (38, 62). Individual maps of functional connectivity from the HTO seeds of each dysplastic subject were compared with the maps of the control subjects in a Crawford modified t test (38). A probabilistic mapping of the overlap of significant individual-subjects t test results was computed (Fig. 2B) 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 at a relatively permissive threshold, such that only two (of four) dysplastic subjects need to have a difference from the controls, at $P < 0.005$ uncorrected, for a voxel to be shown. Individual functional connectivity maps were also computed from seed ROIs defined as spheres (4-mm radius) around the subjects' peak of foot–tool selectivity overlap in the occipito-temporal cortex (Fig. 2D).

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