Congenitally altered motor experience alters somatotopic organization of human primary motor cortex

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Human motor development is thought to result from a complex interaction between genes and experience. The well-known somatotopic organization of the primate primary motor cortex (M1) emerges postnatally. Although adaptive changes in response to learning and use occur throughout life, somatotopy is maintained as reorganization is restricted to modifications within major body part representations. We report of a unique opportunity to evaluate the influence of experience on the genetically determined somatotopic organization of motor cortex in humans. We examined the motor "foot" representation in subjects with congenitally compromised hand function and compensatory skillful foot use. Functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) of M1 revealed that the foot was represented in the classical medial foot area of M1 and was several centimetres away in nonadjacent cortex in the vicinity of the lateral "hand" area. Both areas had direct output to the spinal motor neurons innervating foot muscles and were behaviorally relevant because experimental disruption of either area by TMS altered reaction times. We demonstrate a unique, nonsomatotopically organized M1 in humans, which emerged as a function of grossly altered motor behavior from the earliest stages of development. Our results imply that during early motor development experience may play a more critical role in the shaping of genetically determined neural networks than previously assumed.

fMRI | motor development | motor plasticity | nonsomatotopic | TMS

The adult primary motor cortex (M1) contains the body motor representations arranged in a grossly somatotopic manner. The representation of the leg is located in the most medial aspect of M1 followed in medial to lateral direction by representations of the trunk, arm, hand and face (1). Representations are thought to form during postnatal life through complex interaction between genetic programs and environmental signals (2). Within representations of major body parts, M1 continues to reorganize throughout life in response to experience. Short-term and long-term M1 reorganization is marked by dynamically shifting borders between neighboring representations without the involvement of nonadjacent M1 regions. This leads to enlargements and contractions of partly overlapping motor representations, which occur through, but are also restrained by, an extensive network of horizontal connections. These horizontal connections between different motor output zones are thought to be the neuronal substrate of life-long adaptive changes in M1 (3, 4).

Most prior animal and human studies support this view (3). For example, motor learning was shown to lead to an expansion of those motor representations that were involved in task performance, accompanied by a contraction of task-irrelevant neighboring representations (3, 5, 6). In chronic human lower limb amputees, the motor representation of the remaining proximal stump expanded into the adjacent disconnected area that formerly represented the distal limb (7). If deafferentation occurs during motor development, reorganization seems to follow the same pattern with an enlarged representation of the upper arm (deltoid muscle) resulting from unilateral lower arm amputation in childhood (8–10). However, if the amputation is bilateral and subsequent functional loss compensated for, a different pattern might emerge: Yu *et al.* (11) found foot movement related activation of the classical M1 hand area in 2 subjects with upper limb amputation during childhood and extraordinary compensatory foot dexterity, using fMRI. The functional relevance of this activation remains obscure with two pieces of information missing: first, whether the additional lateral M1 foot area contains corticospinal projections; and second, whether activation in this area is behaviorally relevant.

In human M1, the area that is usually occupied by representation of the hand is very large. Skilled hand movements rely upon the integrity of the corticomotoneural system and direct monosynaptic output from M1 to the spinal alpha motor neurons (12). It is conceivable that a unique M1 organization emerges if input from a major body part such as the hand is missing during development and an alternative motor repertoire is acquired. In such a case, M1 representations may not show the expected somatotopic pattern, but deviate from the known reorganizational principles including violations of somatotopic organization, such as indicated by the finding of Yu *et al.* (11). Nonsomatotopic M1 organization was reported previously in adults with pronounced congenital injury to the corticospinal tract of one hemisphere. In these individuals, the motor representations of both hands were localized in M1 of the nonaffected hemisphere with abnormal monosynaptic ipsilateral projections to the paralyzed hand (13–15).

In this study, we hypothesized that congenitally altered motor behavior due to severely compromised hand function paired with exceptional foot dexterity would produce a nonsomatotopic M1 organization constituted by an additional foot representation in lateral M1. To test this hypothesis, we studied the foot motor representation in 4 individuals with congenital upper extremity malformations due to in utero thalidomide exposure. The individuals participating in this study never fully developed hand function and had acquired unusual foot dexterity early in life. Taken 3 to 7 weeks after conception, thalidomide is known to harm the embryo (16, 17). The most common abnormality is upper extremity dysmelia. In dysmelic malformations, arm length and number of developed fingers is highly correlated (17–19). Because of its bilateral occurrence, severe dysmelia results in the lack of hand

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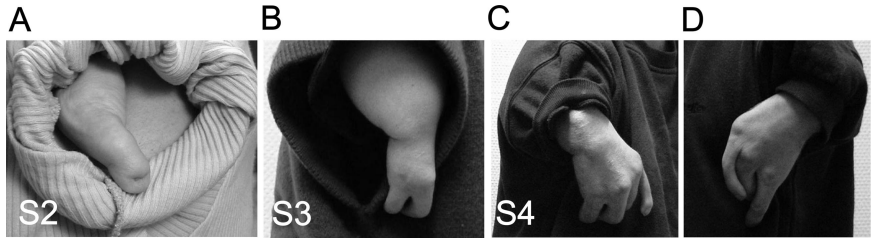

Fig. 1. Upper extremities in dysmelic subjects. (*A*) In Füssler S2, 1 finger attached to the shoulder had developed on the left side, whereas the right side remained amelic. (*B*) In Füssler S3, 2 fingers attached to a foreshortened humerus had developed on the right. One finger attached to the shoulder had developed on the left, similar to *A*. Hand function was severely compromised by the inability to cross arms for bimanual object manipulation. (*C* and *D*) In foot user S4, hands with 4 fingers on the right (*C*) and 3 on the left (*D*) were attached to foreshortened humeri. S4 was able to manipulate objects bimanually. Füssler S1 presented with bilateral amelia (not displayed).

function and forces affected individuals to use their feet for typical hand related fine motor skills of daily life from early childhood. Four subjects (S1–S4), who had developed exceptional skills such as drawing and writing with their feet, were studied (Fig. 1). Only S1–S3 depended on foot use in everyday life because of a severely compromised or entirely missing hand function (Fig. 1 *A* and *B*). These subjects called themselves "Füsslers," a term derived from the German word Füsse (feet). In S4, hand function was largely preserved (Fig. 1 *C* and *D*), but fine motor skills of the feet were as advanced as in the Füsslers (Table S1). We will refer to S4 as "foot-user."

Results

Toe Movement Related fMRI Activation in Two NonAdjacent Areas of M1. To address the question of M1 topography, we first measured brain activity during isolated toe and–if anatomically possible—finger movements, using functional magnetic resonance imaging (fMRI) in the 3 Füsslers, the foot-user, and a control group (see *Methods* and *SI Methods* for details). Electromyography (EMG) during fMRI scanning controlled for strictly isolated movements of either fingers or toes (Fig. S1). Toe movements resulted in activation of medial M1 and the supplementary motor area (SMA) (Fig. 2 *A* and *B*). In Füsslers (S1–S3), isolated toe movements resulted in significant additional activation in lateral M1 compared with the control group ($P < 0.001$ uncorrected) (Fig. 2 *C* and *D* and Tables S2 and S3). This activation was in the vicinity of the anatomically defined omega-shaped hand knob (20) and close to the location activated by finger movements in both Füsslers and the control group (Fig. 2*B* and Table 1). In contrast, the foot-user with largely preserved hand function (S4) did not show this additional lateral M1 activation, neither in comparison with the control group nor in a fixed-effects individual subject analysis, even at a less conservative threshold of $P < 0.01$ uncorrected.

Two M1 Foot Representations with Direct Output to Spinal Motor Neurons Innervating the Foot. In a second experiment, we sought to determine whether corticospinal tract neurons originating in the lateral M1 area connect directly to spinal motor neurons that innervate contralateral foot muscles. We used transcranial magnetic stimulation (TMS) of M1 to elicit motor evoked potentials (MEPs) in a contralateral target foot muscle in Füsslers S2 and S3 and foot-user S4 (21) (see *Methods* for details). TMS of M1 was shown to result in a synchronized discharge of corticospinal tract neurons that have monosynaptic connections with spinal motor neurons (22). Evidence for monosynaptic connections is derived from single motor unit studies in humans where both electrical and transcranial magnetic stimulation of M1 produce first poststimulus time histogram peaks that are comparable to the rising time of the excitatory postsynaptic potential of spinal motoneurons (23).

To map the locations from which TMS elicits MEPs in the target muscle, a 1×1 cm grid with the intersection of the interaural and the nasion-inion lines (CZ) at its origin was marked on the subject's scalp (24). For the targeted muscle, there is usually one small circumscribed area from which the largest MEP responses can be elicited (referred to as a "hot spot") with smaller responses being evoked from adjacent positions (24). In accordance with the medial and lateral M1 activation demonstrated by fMRI, the motor maps of the target foot muscle in Füsslers S2 and S3 were not only extensive but also showed two distinct areas, or hot spots, from which maximal MEP responses were elicited–one medial and one lateral (Fig. 3 *A*–*C*). The close spatial relationship between the lateral foot and classical hand area resulted in MEPs evoked simultaneously in muscles of the foot and the residual finger or shoulder in S2 and S3 respectively (Fig. 3 *C* and *D*). This led to partially overlapping maps when stimulating over lateral M1 positions (Fig. 3). The latencies of the MEPs in the targeted foot muscle (AH) that were evoked by TMS over both the medial and the lateral hot spots were within the 95% confidence interval of reported latencies for this muscle (25–27). Within each subject, these laten-

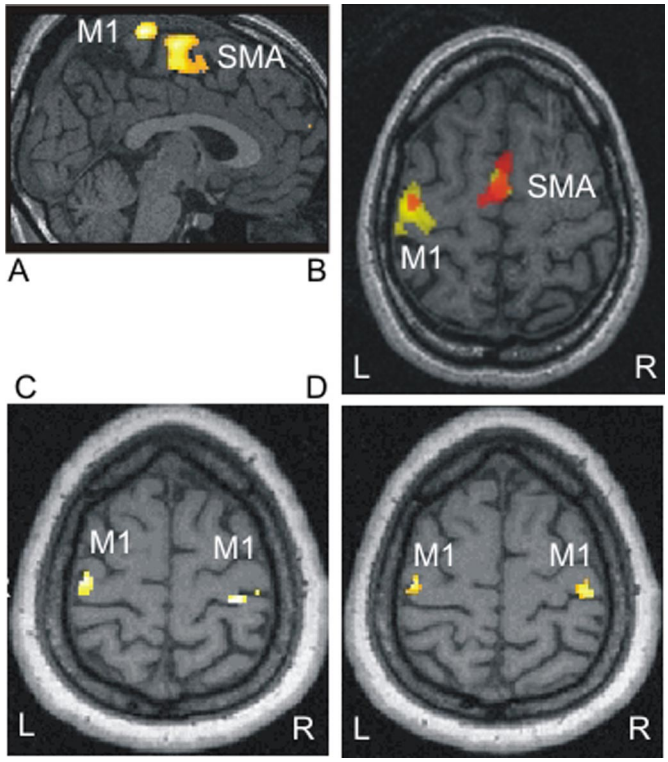

Fig. 2. Toe movement related fMRI activation in subjects with severely compromised hand function (Füsslers). (*A* and *B*) Activation of contralateral M1 foot area and supplementary motor area (SMA) is shown for Füssler S3 (exemplary). Activations are superimposed on the individual T1-weighted MR-image, saggital and axial (z = 62) view. Spatial relationship between activation in the lateral motor cortex because of right finger (yellow) and toe (red) movements in Füssler S3 is illustrated. (*C* and *D*) In Füsslers S1–S3, activation in the precentral gyrus is significantly ($P < 0.001$ uncorrected) stronger for toe movements of the dominant (*C*) and nondominant (*D*) foot when contrasted with 9 control subjects (activation superimposed on the individual T1-weighted MR image of subject S1, z = 66).

Table 1. Toe (dysmelic subjects S1–S3) and finger movement (dysmelic subjects S2 and S3 and control group) -related activations in contralateral lateral M1 areas (close to the anatomically defined hand area)

	Dominant side						Nondominant side					
	toe movements			finger movements			toe movements			finger movements		
Subject	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*
S1	−40	−26	66				44	−24	62			
S2	−22	−22	68							46	−22	56
S3	−38	−18	64	−44	−22	60	44	−20	64	42	−22	66
Control group				−42	−18	60				38	−24	64
S1–S3 vs. control group	−38	−18	66				40	−22	66			

The first four rows of the table give MNI-coordintes and Z-values for lateral M1 area with increased activity when compared to rest. Coordinates for Füsslers S1–S3 are based on single subject fixed- effects analyses. Coordinates for the control subjects were derived from a random-effects group analysis. The last row of the table gives MNI coordinates and *Z* values of lateral M1 area with increased toe movement related activity in Füsslers S1–S3 when compared to the control group (compare SI Table 3). The Euclidian distance between the peak of the lateral activation cluster in Füsslers S1–S3 and the peak activation for finger movements in the control group is 8.2 mm for the dominant and 3.5 mm for the nondominant side. Within subject S3 lateral peak activations related to toe and finger movements were 7.2 mm (dominant side) and 3.5 mm (nondominant side) apart.

cies were of similar magnitude and displayed little variability, indicating similar properties of the corticospinal projections for these two areas (S2: medial M1: 36.44 ± 0.80 ms; lateral M1: 36.57 ± 1.21 ms, S3: medial M1: 38.55 ± 0.94 ms; lateral M1: 38.24 ± 0.93 ms). Because TMS preferentially activates fast conducting corticospinal tract neurons projecting monosynaptically to the spinal motoneuron pool (28, 29), evoked MEPs are likely related to these directly projecting and fast conducting output fibers in lateral and medial areas of the motor cortex. In foot-user S4 with largely preserved hand function, only a single hot spot was identified for the target foot muscle, which was situated over the medial motor cortex (Table S4). Stimulation of more lateral M1 areas did not evoke any measurable evoked responses in this muscle. This was consistent with the fMRI finding only medial M1 area activation related to toe movements in this subject.

Lateral M1 "Foot Area" Behaviorally Relevant for Foot Movements. In a third experiment, TMS was used to disrupt neuronal function in a targeted M1 area. This has been shown to result in measurable delays in motor responses and thereby allows the identification of the stimulated M1 area as functionally relevant for the execution of a specific motor task (30). We reasoned that TMS applied at 140 and 200 ms after a go signal over lateral M1 would delay motor reaction times when Füsslers were asked to respond with their dominant toe in a choice reaction time task (see *Methods* for details). TMS of lateral M1 should not delay toe responses in foot-user S4 or control subjects, but was expected to delay reaction times when a finger was used to respond. TMS applied at 50 ms over lateral M1 served as a control and was expected to shorten response for all tasks and in all subjects because of intersensory facilitation (31). Indeed, TMS of lateral M1 resulted in a significant slowing of reaction times in the toe reaction time task in Füsslers S2 and S3 (Fig. 4*A*). The close spatial relationship between lateral foot and classical hand area was again demonstrated by MEPs evoked simultaneously in muscles of the foot and the residual finger or shoulder in S2 and S3.

In contrast, reaction times for this task remained unaffected by TMS of lateral M1 in foot-user S4 and the control subjects (Fig. 4 *B* and *C*). TMS of lateral M1 significantly delayed reaction times of the finger in both foot-user S4 (Fig. 4*B*) and control subjects (Fig. 4*C*).

Discussion

This study describes a unique expansion of the motor foot representation consisting of the development of 2 distinct nonadjacent foot areas in M1 of adults with severely compromised hand function and highly skilled foot use (Fig. 2 and 3). With this kind of expansion, we demonstrate the potential for genetically determined somatotopic M1 organization to change with experience, thereby identifying behavior as an important factor for the shaping of neuronal networks during motor development.

The similarity of the MEP latencies from lateral and medial M1 area, the similarity of latencies with normative values in the published literature (25, 26, 32), and the small variability of these latencies favor a mono-synaptic corticospinal projection from both the medial and lateral M1 (22, 23). TMS has been reported to activate oligosynaptic pathways as well, such as corticoreticulospinal and corticopropriospinal projections (33). However, it is unlikely that the MEPs shown here for lateral M1 resulted from these oligosynaptic pathways as increases of latencies of >4 ms compared with the monosynaptic route would be expected (33). Activation of slower conducting corticospinal neurons would also result in substantial differences in latencies (23). Because latencies increase with the distance of the stimulation site to the hot spot (34), similarities in latencies between medial and lateral M1 evoked responses exclude the possibility of stimulating one corticospinal tract neuron pool from different sites.

The additional lateral M1 area was functionally relevant for the control of isolated toe movements because experimental disruption of this area by TMS altered reaction times. Our data differs from the previously described use or learning dependent expansions of motor representation into adjacent M1 regions (3). It also differs from previous reports of deafferentation induced reorganization of M1. Rats with neonatal forelimb amputations (35) and humans with upper limb amputations during childhood (8–10) failed to demonstrate comparable large-scale changes. Because amputations in these studies were unilateral and functional compensation of the resulting deficit was not mentioned, this seems to underline the importance of exceptional foot dexterity as the driving force for our findings (further discussed below). An earlier fMRI study in 2 subjects who developed exceptional motor skills of the feet after bilateral upper extremity amputation at 4 and 8 years of age found foot movement related activity in medial and lateral M1, which supports this notion (11). Although corticomotoneuronal projections from the lateral area and the relationship between foot dexterity and lateral M1 activation were not tested, this previous study further suggests that the time window for the development of an abnormal representational pattern such as demonstrated here remains open well into childhood.

It is tempting to speculate that in our Füsslers horizontal fibers integrate medial and lateral foot areas into a new output zone for the control of foot movements, each part of which is relevant for movement execution. However, these fibers would have to span distances of several centimeters, thereby crossing the representa-

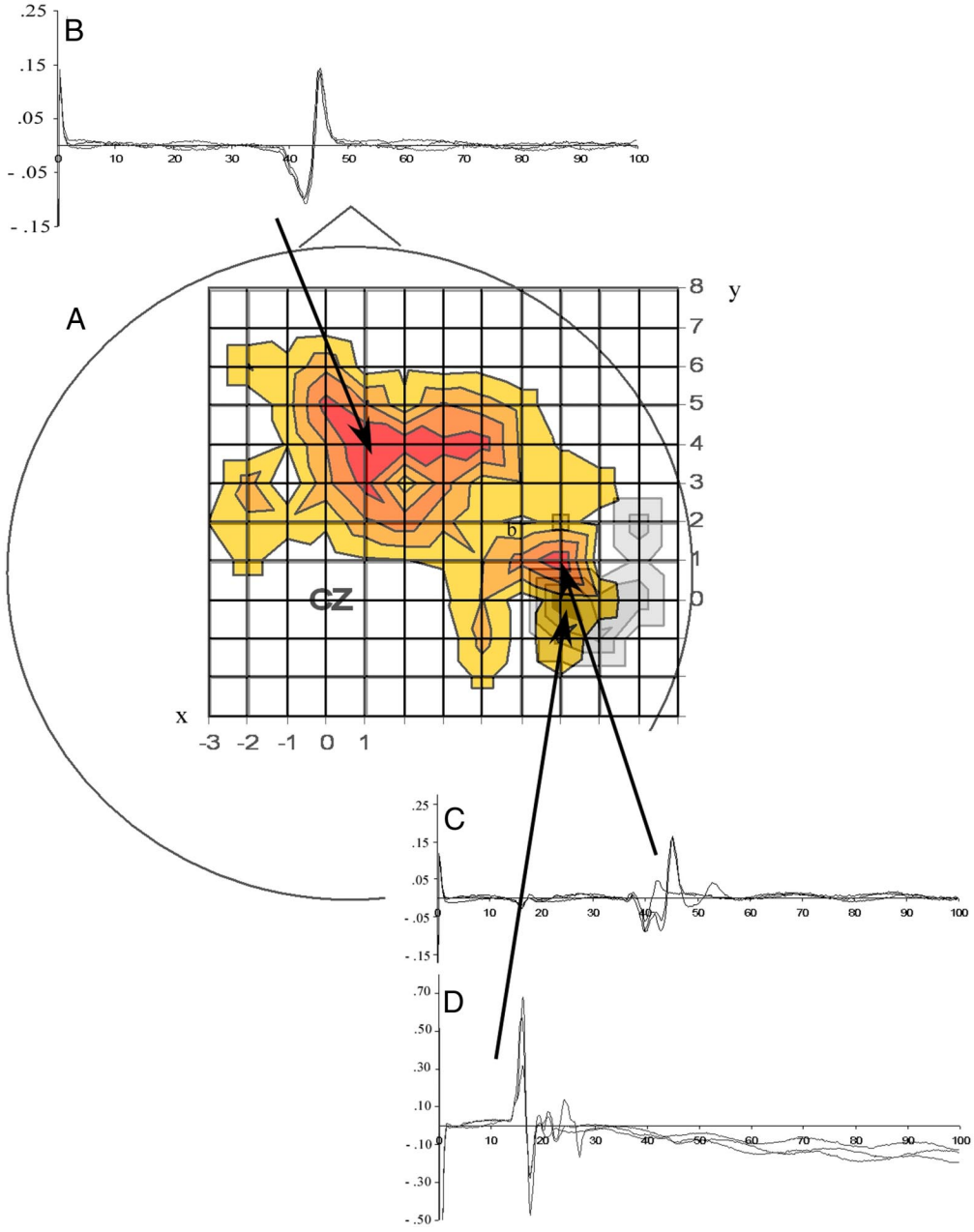

Fig. 3. TMS motor maps and MEPs of abductor hallucis (AH) and a hand muscle in Füssler S3. (*A*) Average of 5 MEPs evoked in the right AH muscle (orange) and right hand muscle (gray). Coordinates refer to positions (in cm) of the center of the coil on the medio-lateral axis (left to right) and fronto-occipital axis (top to bottom) with CZ at 0. MEP data were normalized to the maximum mean amplitude of each map. Positions with a mean amplitude of >20%, >40%, >60% and >80% are indicated by the increasing shading with the darkest shade being the largest amplitude. The map of the AH is superimposed on the map of the hand muscle. (*B*) Overlay of 3 MEPs evoked by TMS applied to the hot spot of the AH, medial M1. (*C* and *D*) Overlay of 3 MEPs evoked by TMS applied to the hot spot of the hand muscle, recorded from AH (*C*) and from the hand muscle (*D*). X axis represents time in ms. Y axis represents amplitude in millivolts.

tions of other major body parts, i.e., leg, trunk and arm. In adult monkeys, horizontal fibers have been shown to spread over distances of up to 8 mm and were abundant only within the representations of major body parts (36). Furthermore, similar latencies for both sites make cortico–cortico projections through horizontal fibers unlikely as several synapses would be included in such a pathway with increased latencies for MEPs evoked from lateral M1. Therefore, purely functional changes within an otherwise normal network of corticocortical and corticospinal fibers appear unsuited to explain our findings.

On the spinal level, axon collaterals of individual corticospinal neurons are known to ramify extensively over several adjacent segments and terminate monosynaptically within multiple motoneuron pools to innervate muscles across multiple joints. However, this phenomenon has only been observed *within* extremities, but not *across* upper and lower extremities (37). Corticomotoneuronal cells with monosynaptic connections to different finger muscles have been found throughout the whole arm area including areas known to contain the shoulder representation, but not beyond (3, 4).

Although our data contains no direct evidence for exceptionally wide-range horizontal connections within M1, it strongly suggests that uncommon corticospinal connections wiring the lateral foot area to the periphery were indeed either established or preserved

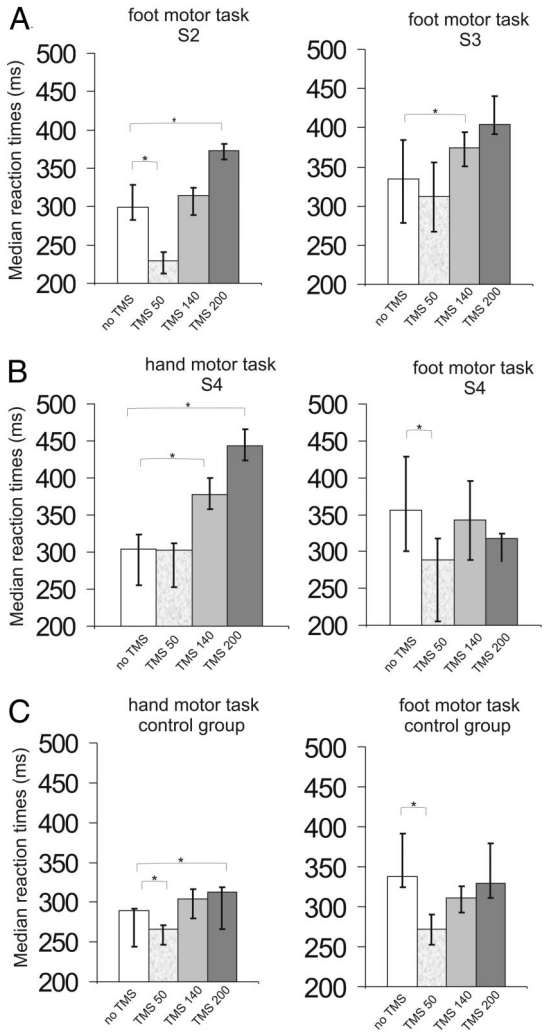

Fig. 4. Effect of TMS on median reaction times for hand and foot motor tasks. Bars indicate the 25th and 75th percentiles for the different TMS conditions. (*A*) Median RTs and percentiles over trials within conditions for the foot motor task in Füsslers S2 (*Left*) and S3 (*Right*). TMS was applied to the lateral M1 foot area. (*B*) Median RTs and percentiles over trials within conditions for the hand and foot motor task in subject S4. TMS was applied to the lateral M1 hand area. (*C*) Median RTs and percentiles across subjects of the control group for the hand (left, $n = 10$) and foot (right, $n = 9$) reaction time task. TMS was applied to the lateral M1 hand area. Significant ($P < 0.05$ 1-tailed uncorrected) decreases (TMS 50) or increases (TMS 140, TMS 200) of reaction times with regard to no TMS condition are marked with asterisks [nonparametric Wilcoxon signed rank tests (control group) or within-subject Mann–Whitney *U* tests (S2-S3)].

during early M1 development (38). Topographic specificity and expansion of corticospinal terminations develops during a prolonged postnatal period in primates (39). Corticospinal projections are target specific (40); e.g., corticospinal projections from an area of the motor cortex that will later become a forelimb area growing toward a cervical spine explant but not to a lumbar explant. Activity dependent modification of sensitivity to ligands that act as guidance cues has been demonstrated. The fate of corticospinal projections that lack their target spinal motor neurons is not known. In subjects S1–S3, it is conceivable that either the lack of function or the lack of cervical spinal motor neurons resulted in a redirection of the growing axon toward the lumbar spinal motor neurons to innervate the foot. This would be consistent with the finding of a somatotopically normal single M1 foot representation in foot-user S4 with preserved hand function. Either the lack of function or the lack of cervical spinal neurons (as a consequence of lacking upper extremities) would then be crucial for the formation of these exceptional corticospinal connections that are then sustained by the exceptional activity of the foot.

A more intriguing explanation builds on the important role of activity-dependent neurotransmission in the competition between motor representations for cortical space during the formation of the mature motor system (41, 42). As indicated by the finding of normal somatotopy with a single M1 foot representation in foot-user S4 with preserved hand function, additional foot representation in lateral M1 only seems to occur when foot dexterity is combined with a seriously compromised hand function during development. It appears that in the competition for the corticospinal fibers that originate in the classical hand area of the lateral motor cortex that the very frequent and highly competent foot use in the Füsslers then prevented an expansion of more adjacently represented body parts. Instead of the common type of neighbourhood expansion, lateral M1 got integrated into a spatially separated doubled foot representation with monosynaptic corticospinal projection to the lumbar spinal motor neurons.

The comparable foot dexterity between Füssler and foot-user indicates that the involvement of lateral M1 is not a prerequisite for the execution of fine motor skills per se, but more sophisticated testing is needed to answer the question of the behavioral gain that may result from 2 motor foot areas.

In this unique group of individuals, our study demonstrates the exceptional role of behavior during early motor development that can lead to the modification of genetically determined representational patterns. Future research is needed to better understand the interaction of genetic programs and experience in motor system development and to provide models with the potential to explain unusual motor organization such as presented here.

Methods

Subjects. Before the study, we screened 60 subjects who had been accepted by the German compensation scheme for having suffered from thalidomide-embryopathy. Four subjects with exceptional foot dexterity and different degrees of upper extremity dysmelia (aged 40–43 years, 3 women) were included in the study. They had no history of any neurological or psychiatric disorder and normal brain anatomy as defined on T1-weighted MR brain images.

Hand function was absent in S1 (because of bilateral amelia) and S2 (Fig. 1*A*), severely compromised in S3 (Fig. 1*B*), but largely preserved in S4 (Fig. 1 *C* and *D*). All had developed fine motor skills of the feet early in life, but only S1–S3 (the Füsslers) reported foot use for activities of daily life. In foot-user S4, foot use was not essential for activities of daily life.

Fine motor skills of the dominant foot were comparable between Füsslers and the foot-user when formally assessed with the Jebsen–Taylor Hand Function Test (JTT) (43) (Table S1), a standardized test designed to test fine motor function of the hand. Only foot-user S4 was able to perform the test with his hand. All normal control subjects (details below) failed to perform the JTT with their feet. All subjects gave written informed consent. The experiments were approved by the Ethics Committee of the Heinrich Heine University, Düsseldorf.

fMRI Experiment. S1–S4 and 12 healthy right-handed controls (aged 26–49, 6 women) participated in this experiment. In one session, subjects were instructed to abduct their big toe (all subjects). In a second session, subjects performed abduction of their index finger (control group) or their best developed finger (S2 - S4). Movements were visually paced at a frequency of 1 Hz and executed with either left or right side. Rest served as the control condition.

To control for undesired coactivation of either hands during toe movements or feet during finger movements, EMG was acquired during fMRI scanning from hand and foot muscles as described in ref. 44. Briefly, EMG was recorded from the abductor hallucis (AH) and the first dorsal interosseus (FDI) muscles. In S2–S4, EMG was recorded from the most prominent finger muscle. EMG recordings showed task related increase in muscle activity for toe abduction in all subjects (Fig. S1). In 3 control subjects, EMG revealed coactivation of the hand during toe movements. Their data were excluded from further analysis.

fMRI and EMG Data Analysis. The functional neuroimaging data were analyzed using SPM99 (Wellcome Department of Imaging Neuroscience, London). Random-effects designs were used to compare task related activation of dysmelic and

control subjects (Tables S2 and S3). Activation due to toe and finger movements was further analyzed using individual fixed-effects designs for S1–S4 (S1–S3, Table 1). Activation with an uncorrected $P < 0.001$ located within a region of interest that covered the sensorimotor and premotor cortices was accepted as significant.

For each experimental condition (LEFT, RIGHT, and REST), the EMG signal between scanning artifacts (periods of 1.2 s) was summed and then averaged. Based on these averages, the ratio between activation and rest was calculated for left and right AH and FDI muscles (44).

TMS Mapping. For S2, S3 and S4, motor evoked potentials (MEPs) were recorded from the AH and the most prominent hand muscle of the dominant side as described in ref. 45. TMS was applied through a round coil (13-cm outer diameter) using 2 Magstim 200 stimulators connected via a Bistim module (Magstim). The motor threshold (MT) was determined from the optimal site for stimulating the target muscle (Table S4). 110% MT intensity was then used to map both muscles' representations. Maps were derived by acquiring 5 MEPs of the target muscle with the stimulator at 110% of MT at locations on the 1×1 cm grid constructed around CZ (24). Mapping proceeded in an anterior–posterior and medial-lateral direction until at least 4/5 MEPs were absent.

Data Analysis for TMS Mapping. The peak to peak MEP amplitudes were averaged for each matrix point, normalized to the maximum response, and then used to construct 2-dimensional maps for visualization (see *SI Methods* for details).

Reaction Time Experiment. S2–S4 and 11 right-handed control subjects (aged 24–50 years, 4 women) participated in this experiment. The performance of a toe and finger motor task was tested in response to a visual cue. For the toe motor task, all subjects were asked to either flex or extend their big toe. For the finger motor task, control subjects responded with abduction or adduction of their index finger, whereas foot-user S4 responded with flexion or extension of his best developed finger. Movements were recorded by a 2-dimensional accelerometer mounted onto the dorsum of the responding digit. Reaction times were defined as the latency between the movement cue and the first peak acceleration in the major movement plane.

EMG activity was recorded from the first dorsal interosseus (FDI) and abductor hallucis (AH) muscles. TMS was applied through a figure-of-eight coil (7-cm outer diameter for each loop) at 120% MT. In Füsslers S2 and S3, the coil was positioned over the lateral motor cortex at the optimal site for stimulating the AH muscle (additional hot spot of AH muscle) while performing the toe motor task. In foot-user S4 and the control subjects, the coil was positioned over the lateral motor cortex at the optimal site for stimulating the FDI muscle while performing either the toe or the finger motor task. TMS was applied on half of the trials 50, 140 or 200 ms after the visual cue. The order of the different TMS trials and no TMS trials was pseudorandomized. TMS applied to M1 at 140 and/or 200 ms after the movement cue was expected to delay motor responses. The time interval of 50 ms served as a control and was expected to shorten response for all tasks and in all subjects because of intersensory facilitation (31).

Data Analysis for Reaction Time Experiment. For the control group, the average reaction times during TMS conditions 50, 140, and 200 were compared with no TMS, using nonparametric Wilcoxon signed-ranks tests based on the intersubject variability. For subjects S2–S4, we used the nonparametric Mann–Whitney *U* test for fixed-effects individual analyses based on the intraindividual variance. Differences with $P < 0.05$, 1-tailed and uncorrected, were accepted as being significant (Fig. 4 *A–D*). One-tailed tests were based on hypothesized RT decreases for TMS 50 and RT increases for TMS 140 and TMS 200.

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