Shrinkage of Somatosensory Hand Area in Subjects With Upper Extremity Dysmelia Revealed by Magnetoencephalography

M. Cornelia Stoeckel, Bettina Pollok, Otto W. Witte, Rüdiger J. Seitz, and Alfons Schnitzler. Shrinkage of somatosensory hand area in subjects with upper extremity dysmelia revealed by magnetoencephalography. J Neurophysiol 93: 813–818, 2005. First published October 6, 2004; doi:10.1152/jn.00749.2004. The effect of peripheral lesions on cerebral somatosensory representations is well studied for experimentally induced amputations and deafferentations acquired later in life. However, few studies have investigated the brain’s capacity for plastic changes in congenital malformations. We studied somatosensory-evoked fields to electrical stimulation of the bordering fingers in 10 subjects with upper extremity dysmelia in comparison with 10 control subjects using a 122-channel whole-head magnetometer. The number of developed fingers varied between two and four in the affected subjects. We localized finger representations in the primary somatosensory cortex and calculated Euclidian distances to estimate the size of the somatosensory hand area. Euclidian distances were significantly smaller in dysmorphic subjects (5.7 mm) than in control subjects (11.6 mm) and were related to the number of the developed fingers on the contralateral hand. In contrast, individual finger representations were not found to be reduced. We suggest that the shrinkage of the somatosensory hand area might be related to the congenital nature of the malformation, to the smaller anatomical hand size in the affected subjects, and/or to use-dependent effects due to impaired hand function.

INTRODUCTION

Representations in primary somatosensory cortex are known to be proportional, not to the size, but to the innervation density and use of body parts (Penfield and Boldrey 1937; Schnitzer et al. 2000). Furthermore, animal experiments and investigations in humans have shown that lesions to the peripheral (Druschky et al. 2000; Elbert et al. 1994; Flor et al. 1995; Merzenich et al. 1983a,b, 1984; Weiss et al. 2000) and CNS (Rossini et al. 1998) are able to induce profound changes in the organization of the somatosensory system both at the subcortical (e.g., Jones and Pons 1998; Rasmussen 1996) and the cortical level (e.g., Grafton et al. 1994; Merzenich 1983a,b, 1984). While in some studies reorganization was observed as a local phenomenon within the representational fields of single body parts (Kelahan and Doetsch 1984; Merzenich et al. 1983a,b), others report evidence for large scale plasticity even across borders of body parts (e.g., Florence et al. 1998; Kamping et al. 2003). For example, studies in monkeys with denervated or amputated fingers have shown cortical area 3b to be occupied by enlarged representations of the neighboring fingers, while the overall size of hand representation remained the same (Merzenich and Jenkins 1993). Similarly, experimentally induced syndactyly does not alter the size of the cortical hand representation (Allard et al. 1991). In contrast, the hand representation was shown to be shrunken in human congenital syndactyly (Mogi- ner et al. 1993). It is conceivable that these differences may reflect the varying capacities of the CNS to reorganize depending on the subjects’ age at time of the lesion (e.g., Hall et al. 1990).

To study the effect of congenital upper extremity damage on the somatosensory hand representation, we investigated subjects with different degrees of congenital upper extremity malformation induced by intrauterine thalidomide exposure.

Thalidomide, when ingested during the third to sixth week of pregnancy, may cause severe malformations in the child during organogenesis (Goldman 1980; Lenz 1962; McBride 1961; McCredie 1975). Upper extremity dysmelia is the most salient symptom in the affected subjects. Because the malformations of arms and hands were innate and had persisted in these subjects for about 40 yr, we expected a smaller hand area for this group compared with normal controls. A shrinkage of the hand representation related to the number of developed fingers on the contralateral hand can be hypothesized. However, we expected the hand representation to be even smaller than can be expected from the anatomical malformation alone, due to the consecutive functional impairment in hand use. For mapping of the somatosensory hand area, we applied magnetoencephalography (MEG) in combination with source modeling. MEG has been shown to be able to reveal plasticity of the human somatosensory cortex noninvasively under diverse conditions such as peripheral deafferentation (Druschky et al. 2000; Flor et al. 1998; Weiss et al. 2000), movement disorders (Elbert et al. 1998), and excessive training (Elbert et al. 1995; Sterr et al. 1998).

Preliminary data were presented elsewhere in abstract form (Stoeckel et al. 2003).

METHODS

We investigated 20 subjects (aged 36–42 yr; mean age, 39.9 yr): 10 (4 males) with normal upper extremities and 10 (6 males) with different degrees of upper extremity dysmelia due to thalidomide embryopathy. Typically, the affected subjects have bilateral malformations, which are predominantly symmetrical (Henkel and Willett 1969). Fingers are characteristically reduced systematically in radial-ulnar order from thumb (1st finger to be missing) to little finger (last finger to remain). In the participating subjects, the number of developed fingers varied between one and four (Table 1). Arms were foreshortened and poorly developed. This was even more pronounced...
in subjects with few residual fingers (Fig. 1). As can be seen in Fig. 1, the palm size was related to the number of developed fingers. Perception thresholds on the fingertips were determined for all subjects using the Semmes-Weinstein nylon monofilaments (Stoelting Co., Wood Dale, IL). None of the subjects reported phantom sensations for the malformed arms and hands. Lower extremities were normal in all subjects.

Prior to the experiment, subjects gave their written informed consent on the basis of the Declaration of Helsinki of 1975. The study was approved by the Ethics Committee of the Heinrich-Heine-University Dußeldorf.

Electrical stimulation was chosen to evoke well-defined and well-described cortical responses (Ploner et al. 1999). MEG is more sensitive to tangential than radial currents, thus electrically evoked responses in SI can be mainly attributed to area 3b (Hari and Forss 1999; Kakigi et al. 2000). The radialmost and ulnarmost fingers on the basis of the first peak will be reported in detail.

Druschky et al. 2000; Elbert et al. 1995, 1997, 1998; Weiss et al. 2000). Because both approaches yielded similar results, only results based on the first peak will be reported in detail.

As in previous studies, we used the Euclidian distance between the stimulated fingers’ representations to estimate the size of the somatosensory hand area (Druschky et al. 2000; Elbert et al. 1995, 1997, 1998; Flor et al. 1998; Maldjian et al. 1999; Sörös et al. 1999). These distances were pooled across hemispheres and compared between groups. Because dysmelia is a bilateral malformation disorder, distances were not compared between hemispheres in individual subjects. The size of the representation of individual fingers was estimated by the cortical baseline-to-peak amplitude and by dividing the size of the hand area by the number of developed fingers on the contralateral hand.

**Results**

Perception thresholds on the fingertips ranged from 16 to 833 mg (median = 170 mg) and were significantly lower in the dysmelic subjects compared with the control group ($P_{2\text{-tailed}} = 0.009$; Mann-Whitney $U$-test). There were no systematic dif-

**Table 1. Number of developed fingers in dysmelic subjects**

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ferences in the perception threshold across fingers in either
group.
Dipoles with localization in contralateral SI were found in
all subjects and conditions. One dipole was excluded from
further analysis because goodness-of-fit was only 76%. Good-
ness-of-fit across all other sources was $93.25 \pm 4.39\%$ (SD).
Latencies to the first peak were shorter in the malformation
group ($27.1 \pm 12.1$ ms) compared with the control group
($36.1 \pm 7.7$ ms). This difference was significant for all stim-
ulated fingers ($P_{1\text{-tailed}} \leq 0.02$) except for the radial finger of
the dominant hand ($P_{1\text{-tailed}} = 0.06$). The shorter latencies were
most likely due to the foreshortened arms in the dysmelic
subjects. Indeed, latencies were significantly (Spearman rank-
correlation $r = 0.4$; $r_{\text{crit}} = 0.38$) related to the length of the
arms as estimated by the number of fingers ($5$ fingers = no
foreshortening; $2$ fingers = severe foreshortening).

Figure 2 shows the localization of dipoles related to the
stimulation of D1 and D5 in one representative control subject
together with the corresponding magnetic field distributions.

SI sources in the dysmelic subjects had similar localization
and orientation but were closer to each other (Fig. 3). The
average Euclidian distance of the dipoles was $11.6 \pm 5.3$ mm
in subjects with normal upper extremities (pooled across hemi-
spheres) and was significantly ($P_{1\text{-tailed}} < 0.001$) reduced to
$5.7 \pm 1.7$ mm in subjects with malformed upper extremities
(Mann-Whitney $U$-test).

Across both hemispheres, distances were significantly corre-
lated with the number of fingers on the contralateral hand ($r = 0.58$, corrected for ties according to Siegel and Castellan
1988; $r_{\text{crit}} = 0.38$; Fig. 4).

The mean size of individual finger representations, the
“space per finger” was $2.3$ mm in the control group and $1.9$ mm
in the dysmelic subjects. There was no difference concerning
the space per finger across groups ($P_{2\text{-tailed}} = 0.33$). Average
baseline-to-peak amplitudes were $10.8 \pm 4.37$ nA in the
control group and $11.31 \pm 6.27$ nA in the dysmelic subjects.
Amplitudes were not significantly different across groups for
any of the four stimulated fingers ($P_{2\text{-tailed}} \geq 0.45$).

Average localization of finger representations followed the
known somatotopy in the control group (Fig. 5). In the dys-
melic subjects, the average localizations of the radial- and
ulnarmost fingers were so close together that these appeared
virtually identical in the inferior-superior direction. The lack of
a clear somatotopic arrangement in this group was probably
due to the proximity of finger representations in relation to the
localization accuracy of the MEG method.

**DISCUSSION**

Our data show a significantly reduced hand representation in
subjects with congenitally malformed upper extremities in
combination with improved perceptual detection capacities
on the fingertips. The reduction in size is clearly different from
experimentally induced conditions in adult monkeys (Allard et

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**FIG. 2.** Dipole modeling and source localization in 1 representative control
subject on the basis of somatosensory-evoked fields (SEFs) related to thumb
(left) and little finger (right) stimulation. A: sources superimposed on the
individual anatomical MR image (top: axial slices; bottom: sagittal slices).
Tails indicate the orientation of the dipoles. B: magnetic field distribution at
time of 1st peak. Contour step size = 10 fT. Black lines indicate magnetic flux
emerging from the head, whereas gray lines represent entering magnetic flux.
Arrows show direction of the current flow of the fitted dipole.

**FIG. 3.** Left: dipole localization in 1 representative control subject. Right:
dipole localization in 1 representative subject with upper extremity malforma-
tion (with 3 fingers on each side).

**FIG. 4.** Euclidian distances between representations of bordering fingers
plotted vs. number of developed fingers on the contralateral hand (▲, dysmelic
subjects; ◆, control subjects).
were either amputated (Merzenich and Jenkins 1993) or previous experimental studies. In the latter, middle fingers dysmelia syndrome is different from the lesions produced in the former for congenital disorders. When middle fingers are amputated, the preserved bordering finger representations might have prevented the invasion of neighboring body part representations and the shrinkage of the hand area. Likewise, the size of the hand representation might appear normal in congenital conditions when middle fingers are missing. Further support for this hypothesis comes again from the study of Mogilner et al. (1993), where bordering fingers were involved in the complex congenital malformation that was associated with a shrunken hand representation.

Interestingly, in the study of Mogilner et al. (1993), the hand area was shown to expand substantially within 1 mo after surgical separation of the webbed fingers. This substantial change occurred in adulthood and can be seen as use-dependent plasticity brought about by the newly gained functional independence of the fingers. Use-dependent plasticity is also another strong candidate to explain a reduced hand representation in our dysmelic subjects. Just as excessive and dedicated training results in larger somatosensory representations (Braun et al. 2000; Elbert et al. 1995; Stoeckel et al. 2004), the disuse of body parts was followed by a shrunken motor representation within weeks (Liepert et al. 1995). Likewise, a reduced motor representation after stroke was shown to return to normal size after a functionally effective, rehabilitative training (Liepert et al. 2000). The dysmelic subjects participating in this study reported to accomplish almost all everyday actions with their hands. Compensatory use of the feet was restricted to very few actions in all but one subject (S10; compare Stoeckel et al. 2000). The dysmelic subjects participating in this study were able to accomplish opposition movements in all but one subject (S10; compare Stoeckel et al. 2004). However, due to the changed anatomy, thalidomide-damaged subjects with malformed upper extremities use their hands differently (Sievert 1965). Opposition movements (pinch grip) are only possible between neighboring fingers because the thumb is always missing. In normal subjects, the thumb has many degrees of freedom for movements and is able to accomplish opposition movements with all other fingers of a hand. Therefore the thumb is the most important finger for sensorimotor hand function such as object manipulation (Kunesch et al. 1989; Seitz et al. 1991). Consequently, the less elaborate hand use might primarily explain or contribute to the reduced hand area in the dysmelic subjects. However, a shrinkage was only shown for the entire hand area, while baseline-to-peak amplitudes and the estimated space per finger indicate normal sized individual finger representations in the dysmelic subjects. Higher perceptual detection capacities in the dysmelic subjects compared with the control group would suggest even larger than normal individual finger representations in these subjects.

However, there are alternative explanations for the differences between our findings and previous studies. First, the dysmelia syndrome is different from the lesions produced in previous experimental studies. In the latter, middle fingers were either amputated (Merzenich and Jenkins 1993) or webbed (Allard et al. 1991). In contrast, bordering fingers beginning with D1, D2, etc. are characteristically missing in dysmelia. Because there are no experimental studies in which bordering fingers have been amputated, we don’t know whether this would produce a shrunken hand area in later life as seen in this study for a congenital disorder. When middle fingers are amputated, the preserved bordering finger representations might have prevented the invasion of neighboring body part representations and the shrinkage of the hand area. Likewise, the size of the hand representation might appear normal in congenital conditions when middle fingers are missing. Further support for this hypothesis comes again from the study of Mogilner et al. (1993), where bordering fingers were involved in the complex congenital malformation that was associated with a shrunken hand representation.

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The enlargement of the somatosensory hand representation as described by Elbert et al. (1995) and Mogilner et al. (1993) was most likely based on an enlargement and/or a separation of individual finger representations. Whether the shrinkage of the hand area was caused by the early onset of the malformation disorder, anatomical peculiarities, or life-long use-dependent effects cannot be decided on the basis of these data. Furthermore, an interaction of all of these factors cannot be excluded.

Another unresolved question is whether a smaller hand area is paralleled by enlarged representations of the other body parts. For example, in patients with facial nerve palsy, the arm representation expanded into the face area (Rijnjtes et al. 1997). While the neighboring face area is a possible candidate for enlargement, an invasion by the neighboring arm representation seems unlikely. The length of the arms is typically also reduced in the dysmelia syndrome and covaries with the number of fingers (Henkel and Willert 1969). Therefore the arm representation itself is also expected to be reduced. An overall shift in favor of an enlarged foot representation is rendered unlikely by findings of Stoeckel et al. (2004), because in a group of dysmorphic subjects with two to four developed fingers, the foot representation was not shown to be enlarged or shifted. It seems even possible that a silent area remains in congenital malformation syndromes because reorganization was shown to be more extensive in acquired than congenital amputation (Flor et al. 1998; Jain et al. 2000, 2001). Alternatively, the entire SI area could be smaller in the dysmorphic subjects. This question is difficult to address with MEG due to methodological limitations. We suggest that this issue would best be addressed in a morphometric study.

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References


