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

M. Cornelia Stoeckel,1 Bettina Pollok,1 Otto W. Witte,2 Rüdiger J. Seitz,1 and Alfons Schnitzler1

1Department of Neurology, University Hospital, Düsseldorf; and 2Department of Neurology, University Hospital, Jena, Germany

Submitted 23 July 2004; accepted in final form 29 September 2004

Stoeckel, M. Cornelia, 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; Schnitzler 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; Rasmusson 1996) and the cortical level (e.g., Garraghty 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 (Mogilner 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; McCrede 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 Duesseldorf.

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 each hand were stimulated via ring electrodes (CH Medizintechnik, Dusseldorf, Germany) using two Grass S88 constant voltage stimulators (Grass Medical, Quincy, MA), which delivered square-wave stimuli at a frequency of 5 Hz and of 0.3-ms duration. Wet electrodes were used for better conductance and were placed at the proximal interphalangeal joints, the cathode always being proximal. Fingers were used for better conductance and were placed at the proximal interphalangeal joints, the cathode always being proximal. Fingers were stimulated in turn for trains of 20-s duration. Each recording session had a duration of ~3 min resulting in ~450 epochs per finger. Somatosensory-evoked fields (SEFs) related to the onset of the electrical stimuli were measured using a 122-channel whole-head neuromagnetometer (Neuromag, Helsinki, Finland) situated in a magnetically shielded room. Stimulus intensities were chosen just below the pain threshold and were at least twice the sensory threshold. Subjective perception of the intensities was reported by the subjects to be equal across all fingers. The average stimulus intensity across all subjects and fingers was 15.6 ± 4.5 (SD) V. There was no difference in stimulus intensities or evoked amplitudes for any of the two stimulated fingers of each hand across groups (Mann-Whitney U-tests for independent samples; \( P_{\text{2-tailed}} \geq 0.45 \)).

Data were filtered on-line with a band-pass filter of 0.03–330 Hz and digitized at a sampling rate of 1,011 Hz. Eye blinks were controlled by vertical electrooculogram, and contaminated trials were rejected.

The signal was averaged off-line for each finger separately. Epochs were averaged from ~230 to 230 ms with regard to stimulus onset and using a high-pass filter of 1 Hz. For further analysis, data were smoothed with a 145-Hz low-pass and a 50-Hz notch filter.

For co-registration of MEG data with the individual anatomy, a T1-weighted magnetic resonance tomodography (MRT) image with 1 × 1 × 1 mm spatial resolution was acquired in each subject using a Vision scanner (Siemens, Erlangen, Germany). Data were aligned to the individual MRT image using the magnetic signals from four coils placed on the scalp during the measurement and three anatomical landmarks (nasion and bilateral periauricular points). The position of the coils with regard to the landmarks had been digitized (Isotrack fastrak, Polhemus Navigation Sciences, Colchester, VT) outside the shielded room before MEG data acquisition. Using a spherical volume conductor model, single equivalent current dipoles were used to explain the evoked fields. A selection of channels around the area with the largest response and the first peak with clear bipolar distribution were used for dipole fitting in SI of the contralateral hemisphere. Only sources explaining ≥80% of the field variance (goodness-of-fit) when the dipole moment was maximal were accepted for further analysis. In a second approach, single dipoles were fitted when local field power was maximal in a time window ranging from 15 to 120 ms (cf. 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 \(P_{\text{2-tailed}} = 0.009\); Mann-Whitney U-test). There were no systematic dif-

<table>
<thead>
<tr>
<th>Number of developed fingers in dysmelic subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Fingers</td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>S1</td>
</tr>
<tr>
<td>S2</td>
</tr>
<tr>
<td>S3</td>
</tr>
<tr>
<td>S4</td>
</tr>
<tr>
<td>S5</td>
</tr>
<tr>
<td>S6</td>
</tr>
<tr>
<td>S7</td>
</tr>
<tr>
<td>S8</td>
</tr>
<tr>
<td>S9</td>
</tr>
<tr>
<td>S10</td>
</tr>
</tbody>
</table>

**FIG. 1.** Subjects with different degrees of upper extremity malformation.
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%. Goodness-of-fit across all other sources was 93.25 ± 4.39% (SD). Latencies to the first peak were shorter in the malformation group (27.1 ± 12.1 ms) compared with the control group (36.1 ± 7.7 ms). This difference was significant for all stimulated 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 \( r_s = 0.4; r_{\text{crit}} = 0.38 \)) related to the length of the arms as estimated by the number of fingers \( (5 \text{ fingers} = \text{no foreshortening}; \ 2 \text{ fingers} = \text{severe foreshortening}) \).

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 ± 5.3 mm in subjects with normal upper extremities (pooled across hemispheres) and was significantly \( (P_{1\text{-tailed}}<0.001) \) reduced to 5.7 ± 1.7 mm in subjects with malformed upper extremities (Mann-Whitney \( U \)-test).

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

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 ± 4.37 nA in the control group and 11.31 ± 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 dysmelic 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
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
ences between our findings and previous studies. First, the observed here needed the considerably long period of 40 yr to emerge. Moreover, the malformation of the hand had persisted in our subjects for about 40 yr. As far as we know there are no studies neither in animals nor humans where an acquired lesion dates back a similar amount of time. We cannot decide from our data whether the overall outline of the hand area possesses less potential for changes in later life or whether the changes we observed here needed the considerably long period of 40 yr to emerge.

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.

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. 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 (Kunisch et al. 1989; Sieitz 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. Larger finger representations together with a shrinkage of the overall hand area imply overlapping representation cortical fields, which is known to result in reduced localization capacities (Mogilner et al. 1993; Sterr et al. 1998). However, localization capacities across different fingers were described to be normal in the dysmelic subjects (Stoeckel et al. 2004).

We assume that the lower detection thresholds were most likely due to a lower degree of horny skin on the finger tips rather than to larger cortical finger representations.

FIG. 5. Mean localization and SE for representations of the radial finger with regard to the ulnar finger (origin) in control (●) and dysmelic (○) subjects. Coordinates were pooled across hemispheres whereby representations of left fingers were mirrored. x, medial to lateral; y, anterior to posterior; z, inferior to superior.
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 dysmERIC 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 dysmERIC 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. 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. 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.

REFERENCES


