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Report

Immobilization Impairs Tactile Perception and Shrinks Somatosensory Cortical Maps

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Summary

Use is a major factor driving plasticity of cortical processing and cortical maps. As demonstrated of blind Braille readers and musicians, long-lasting and exceptional usage of the fingers results in the development of outstanding sensorimotor skills and in expansions of the cortical finger representations. However, how periods of disuse affect cortical representations and perception in humans remains elusive. Here, we report that a few weeks of hand and arm immobilization by cast wearing significantly reduced hand use and impaired tactile acuity, associated with reduced activation of the respective finger representations in the somatosensory cortex (SI), measured by functional magnetic resonance imaging. Hemodynamic responses in the SI correlated positively with hand-use frequency and negatively with discrimination thresholds, indicating that reduced activation was most prominent in subjects with severe perceptual impairment. We found, strikingly, compensatory effects on the contralateral, healthy hand consisting of improved perceptual performance compared to healthy controls. Two to three weeks after cast removal, perceptual and cortical changes recovered, whereas tactile acuity on the healthy side remained superior to that on the formerly immobilized side. These findings suggest that brief periods of reduced use of a limb have overt consequences and thus constitute a significant driving force of brain organization equivalent to enhanced use.

Results

Imaging studies provided compelling evidence that training and enhanced use of a body part cause plastic reorganizational changes in the functional brain architecture of string players [1], blind Braille readers [2–4], and musicians [5, 6]. These findings in humans corroborated the concept of use-dependent plasticity, derived from animal studies [7–12], according to which changes in cortical maps depend on the amount of use that an individual allocates to conform to the current requirements of environmental constraints. Here, we address the issue of how enforced disuse, resulting from an everyday-life situation of wearing a cast for several weeks as a result of a hand or arm fracture, affects perceptual performance and reorganization of the somatosensory cortex in an otherwise intact nervous system.

We first confirmed the prevailing assumption that immobilization reduces the amount of use of the immobilized hand as compared with the healthy hand. During cast wearing, we recorded motion of the arms in two planes with the use of accelerometer sensors fixed to the wrists of both of the subject's arms (mean duration 3.23 ± 0.82 hr [mean ± SD]).

Healthy, right-handed, age-matched controls showed acceleration values of 28.67 ± 1.57 mG for the right hand and 24.60 ± 2.23 mG for the left hand. The side-to-side difference was 5.88 ± 1.37 mG (paired t test: $p < 0.0021$). In contrast, the group of right-handed, cast-wearing subjects showed significantly reduced movement activity for the immobilized hand (15.68 ± 2.01 mG) in comparison to the healthy hand (37.73 ± 3.60 mG; paired t test: $p < 0.0001$), with a mean side-to-side difference of 17.67 ± 3.56 mG (paired t test: $p < 0.0001$). Accordingly, immobilization caused a significant decrease of acceleration values in comparison to the left (t test: $p = 0.0026$) and right hand of healthy controls (t test: $p < 0.0001$). Importantly, acceleration values for the healthy hand of cast patients were substantially increased in comparison to the left (t test: $p = 0.0066$) and right (t test: $p < 0.04$) hand of control subjects (Figure 1). These data substantiate cast patients' less-than-normal use of their immobilized hand, supporting the assumption that immobilization acts to enforce disuse. However, the reduced use of the immobilized hand is compensated for by a more frequent use of the other, healthy hand (Figure 1).

To demonstrate perceptual implications of immobilization, we assessed tactile acuity by measuring spatial two-point discrimination thresholds on the tip of the index finger [13–16]. For the healthy controls, we found no difference in threshold between the right and the left fingers (paired t test: $p = 0.28$, $n = 36$ Figure 2). In contrast, discrimination thresholds for the immobilized index finger, but not for the healthy index finger, were significantly higher (Figure 2) in cast-wearing subjects, indicating a significant impairment of discrimination abilities caused by, on average, 22 days of immobilization (paired t test: $p < 0.0001$), with a side-to-side difference between the healthy and the immobilized index finger of 0.44 ± 0.43 mm (paired t test: $p < 0.0001$).

We also evaluated whether the side or duration of cast wearing affected the observed changes in discrimination. All

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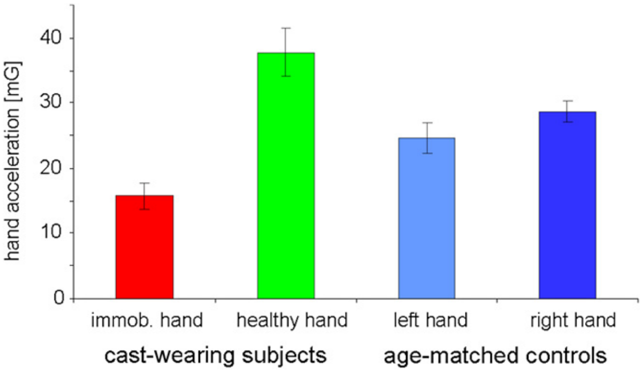

Figure 1. Differences in Hand and Arm Acceleration between Cast-Wearing Subjects and Healthy, Age-Matched Control Subjects

A comparison between cast-wearing subjects and healthy controls revealed a significant reduction in hand and arm acceleration of the immobile hand (red) and a significantly enhanced frequency of use for the healthy hand (green) in cast-wearing patients in comparison with the left and right hand (light and dark blue) in healthy controls (paired t test: $p < 0.0001$ for all conditions).

subjects were right handed; however, it was unclear whether it made a difference if the dominant or the nondominant hand was immobilized. We observed no significant differences in the performance of the immobilized hand to either the side of cast wearing ($p = 0.9908$) or the duration of cast wearing ($p = 0.4727$). However, performance of the healthy hand correlated with the duration of cast wearing, both for differences to values predicted by the control group (Pearson's $r = -0.3679$, $p = 0.045$) and for differences to values predicted within the group ($r = -0.46$, $p = 0.010$). Accordingly, whereas impairment in performance was independent of side and duration, improvement of the healthy hand depended on the duration of cast wearing.

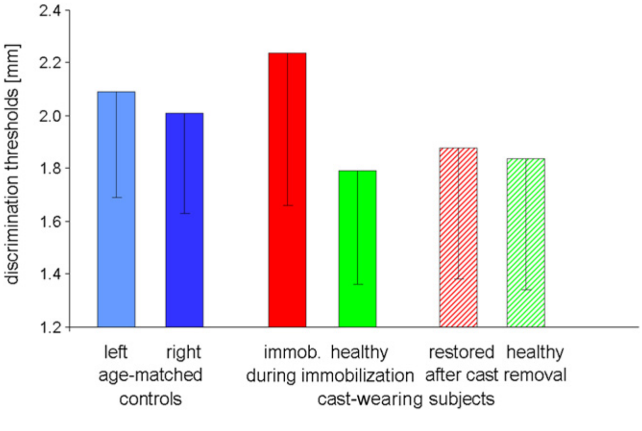

Figure 2. Effects of Immobilization on Tactile Spatial Discrimination

Tactile discrimination thresholds of the index fingers (IFs) in subjects wearing a cast on their hand and arm ($n = 31$), resulting in immobilization of the hand and finger, in comparison with age-matched controls ($n = 36$). Cast-wearing subjects showed higher discrimination thresholds of their immobilized IF in comparison with the right or left IF of age-matched controls (paired t test: $p < 0.0001$). However, discrimination performance of the healthy IF in cast-wearing subjects was better than that of age-matched controls. Two to three weeks after cast removal, discrimination performance of the immobilized hand's IF recovered to the thresholds observed for the healthy hand of cast-wearing subjects and age-matched controls.

To assess long-term effects of immobilization, we retested tactile acuity two to three weeks (18.0 ± 6.8 days) after cast removal. We found that discrimination thresholds of the immobilized hand returned to normal (paired t test $p < 0.0001$; $n = 29$; Figure 2), meaning that there was no significant difference between the healthy and the previously immobilized hands after cast removal (paired t test $p = 0.780$).

To facilitate better understanding of the recovery process, we compared cast patients with controls for changes in discrimination thresholds, separately for left- or right-hand immobilization. With right-hand immobilization ($n = 8$), the healthy hand showed superior tactile discrimination that persisted after two weeks of cast removal ($p = 0.0249$), indicating a sustained compensatory effect. This analysis confirmed that for right-hand immobilization, the thresholds on the immobilized index finger recovered to values typically found in controls two weeks after cast removal. In contrast, for left, nondominant hand immobilization ($n = 6$), the thresholds of both the immobilized and the healthy finger recovered to a normal performance typically found in age-matched subjects.

Given the perceptual changes after immobilization, we then asked how immobilization affects cortical maps. To assess possible blood-oxygen-level-dependent (BOLD) signal changes within the somatosensory cortex after immobilization, we performed fMRI measurements on two subpopulations of 12 (4 and 8) subjects in total. Two of the subjects in the first subgroup wore a cast on their right, and two wore a cast on their left hand, for a mean duration of 2.3 ± 0.5 (mean ± SD) weeks (Figures 3 and 4). Tactile discrimination thresholds of these subjects were in the same range as those described for the entire population investigated. FMRI measurements were performed once during cast wearing after two weeks of immobilization. Additionally, in three of these subjects, a second imaging session was performed two weeks after cast removal for study of the reversibility of immobilization-induced changes. The first imaging session revealed that after two weeks of immobilization, the representation of the immobilized index finger in the primary somatosensory cortex (SI) decreased (Figures 3 and 4). Cluster size of the activation evoked by stimulation of the immobilized index finger was distinctly smaller in comparison with the healthy control index finger (immobilized finger: cluster-level = 3 voxels, T score = 5.46; healthy finger: cluster level = 17 voxels, T score = 5.64; $n = 4$; Figure 4).

The results of the group analysis are shown in the estimated statistical parametric maps of the fixed-effect analysis (Figure 4) and reveal focused SI activation in the postcentral gyrus ($n = 4$). The second imaging session two weeks after cast removal revealed no hemispheric differences in BOLD signal extension and SI intensity (Figure 4), indicating the reversibility of immobilization-induced cortical changes (formerly immobilized index finger: cluster level = 23 voxels, T score = 6.72; contralateral, healthy index finger: cluster level = 17 voxels, T score = 5.84).

To corroborate the covariation of the behavioral and perceptual measures, as well as the fMRI changes, eight additional right-handed subjects (aged 18 to 48 years), who wore a cast on their right hand, were analyzed for quantitative indices of the relationship between changes in BOLD signals and hand use and tactile discrimination. We used the mean signal intensity (MSI) as the statistical parameter for the quantification of the BOLD response. During immobilization, we found significant individual differences between the healthy and the cast-wearing side for both parameters (mean signal

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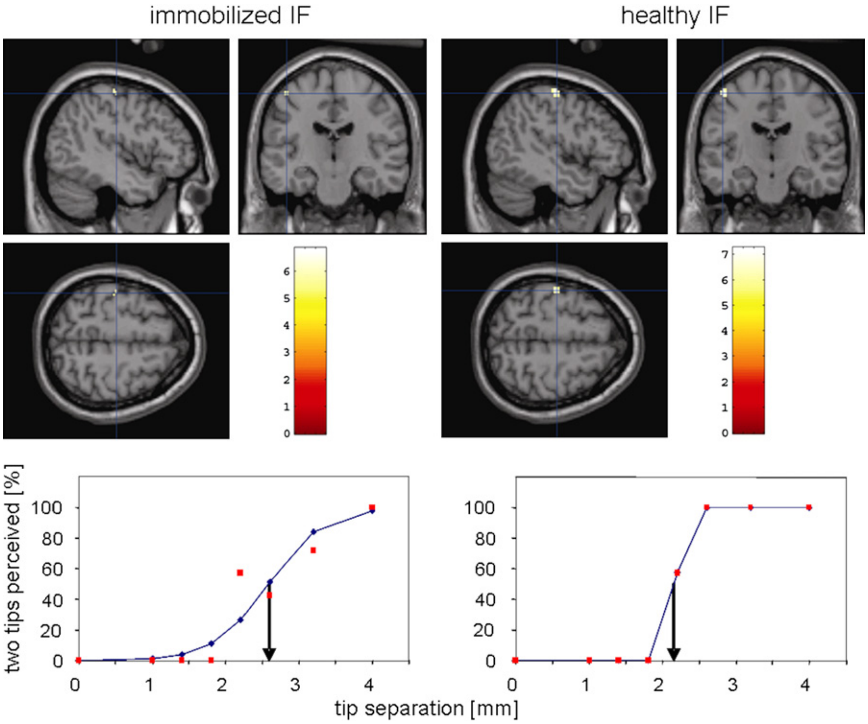

Figure 3. Activation of Somatosensory Cortical Finger Representation in a Cast Patient

BOLD signals detected in the primary somatosensory cortex (SI) of a single subject, showing the effects of two weeks of right-side immobilization on the cortical index finger representation of the immobilized (top left) and healthy (top right) hands. Activations are projected on the left hemisphere on an axial, sagittal, and coronal T1-weighted, normalized MRI slice. Significance was determined with p = 0.000001 used for peak height (immobilized and healthy index finger [IF]). The activations obtained after electrical stimulation of the IFs revealed decreased BOLD activity for the IF in comparison with the healthy finger (immobilized IF SI parameters: cluster level = 7 voxels; T score = 6.01, MNI template coordinates −44,−20,60 [x,y,z (mm), Brodmann area 3]; healthy IF SI parameters: cluster level = 28 voxels; T score = 7.24, MNI template coordinates −46, −16,58 [x,y,z (mm), Brodmann area 3]), indicating that enforced disuse of a limb alters the cortical map within the SI. At the bottom of the figure, psychometric functions illustrate the impact of two weeks of immobilization on tactile discrimination thresholds for the subject shown above. Correct responses in percentages (red squares) are plotted as a function of separation distance together with the results of a logistic regression line (blue with blue diamonds). Shown are 50% levels of correct responses, as well as tactile discrimination thresholds. In comparison with the those of the healthy IF (bottom right), discrimination thresholds of the immobilized IF increased (bottom left) by about 0.4 mm (2.58 mm versus 2.18 mm), indicating impaired tactile performance of the immobilized hand.

intensity: healthy side MSI = 0.141 ± 0.171, cast-wearing-side MSI = −0.139 ± 0.199; paired t test p = 0.03).

To obtain a quantitative index for immobilization-induced changes in behavior and BOLD signals, we performed a correlation analysis. We found a positive correlation between the BOLD signal (MSI) and frequency of hand use (including pre and post data, healthy and cast hand), indicating that minimal hand use was associated with the largest reduction in cortical activation, whereas patients showing small changes in hand use showed only small changes in activation (MSI: r = 0.42, p = 0.034;). Between the BOLD signal (MSI) and discrimination thresholds (including pre and post data, healthy and cast hand) we observed a negative correlation, indicating that the most severe increase of discrimination thresholds was associated with the largest reduction of cortical activation and vice versa (MSI: r = −0.47, p = 0.0099).

Discussion

In the motor domain, immobilization induces severe muscle atrophy, as well as changes in motor cortex excitability [17], firing rates of human motor units [18], and contractile properties of skeletal muscles [19]. In dynamic immobilization, which allows for passive but not active movements, a recruitment of parietal and cingulate activations has been observed [20]. Through transcranial magnetic stimulation that mapped out the area of the motor cortex, a reduction in the size of the cortical muscle representation of the immobilized limb in the primary motor cortex was reported, in which the amount of shrinkage correlated with the duration of cast wearing [21]. We show that significant alterations due to immobilization are not limited to the motor system; in addition, tactile perception is impaired in parallel with a reduced activation in the somatosensory cortex.

The impact of reduced use on cortical representational maps has been addressed before in animal models. After 7 to 14 days of forelimb immobilization in rats, the area extent of the cutaneous map of the casted forepaw decreased [22]. Within a few days of impairment of locomotion behavior via cutting of a hindlimb tendon, shrinkage of the cortical hindlimb map was reported [23]. Space-flight conditions or hindlimb suspension completely prevent the use of limbs, resulting in modified posture and gait, which was paralleled by a reduction in the number of GABA-immunoreactive cells [24], indicating changes in sensory processing. In patients with complex regional pain syndrome (CRPS) and intractable pain, cortical maps on the primary (SI) and secondary somatosensory cortex (SII) contralateral to the affected limb have been reported to be significantly reduced in size, which was paralleled by an impairment of the two-point discrimination thresholds, all of these changes developing with reduced use of the affected limb [25]. Sensorimotor retuning led to a persistent decrease in pain intensity, which was accompanied by a restoration of the impaired tactile discrimination and regaining of cortical map size in the contralateral SI and SII.

In addition, a body part will be used less frequently when it is damaged after lesion or nerve injury. Electrophysiological recordings in adult monkeys revealed that depriving a large expanse of cortex by transecting both the median and the ulnar nerves of the hand induced a reversible large-scale cortical reorganization [26–28]. A large body of literature also indicated enlargement of the amputated limb area after amputation [29, 30]. In individuals suffering from stroke, enlargement of affected representations is correlated with impaired use of the paralyzed limb [10, 31]. In these forms of map

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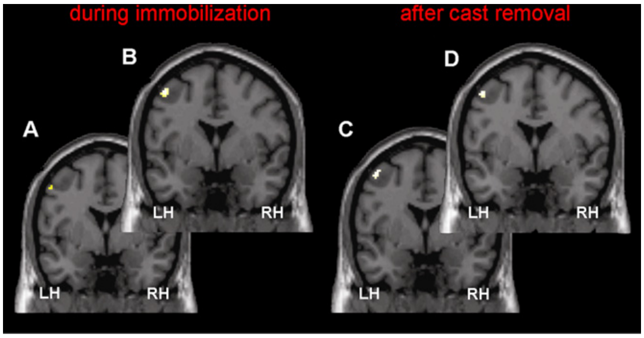

Figure 4. Fixed-Effect Analysis of BOLD Activity within the SI during Immobilization and Two Weeks after Cast Removal

Significance was determined with the use of p = 0.000001 for peak height (immobilized index finger [IF] and healthy IF). BOLD signals measured in the primary somatosensory cortex (SI) are projected on the left hemisphere of coronal T1-weighted MRI slices (LH: left hemisphere, RH: right hemisphere) for better comparability.

(A and B) Activation for the immobilized IF during immobilization (A) and for the contralateral, healthy IF during immobilization (B). n = 4.

(C and D) Activation for the restored IF two weeks after cast removal (C) and for the healthy IF two weeks after cast removal (D). n = 3.

Activation during immobilization: SI parameters: cluster level = 3 voxels; T score = 5.46; SI (contralateral) parameters: 52 voxels; T score = 7.57. Healthy IF representation during two weeks of immobilization: SI parameters: cluster level = 17 voxels; T score = 5.64.

Two weeks after cast removal, fixed-effect analysis (n = 3) revealed recovery of changes in BOLD signal extension and intensity in SI, representing the restored IF. SI parameters: cluster level = 23 voxels; T score = 6.72. Healthy IF representation two weeks after cast removal: SI parameters: cluster level = 17 voxels; T score = 5.84.

No significant changes in activation pattern were found for the secondary somatosensory cortex.

expansion, intact cortical territories take over those regions that are deprived of input. Therefore, plastic changes evoked by nerve damage or central injuries are characterized by a confound of injury-dependent reorganization and those changes arising from changes in the amount of use.

On the other hand, there is convincing evidence that enhanced use and long-term training improve perceptual performance, parallel with an expansion of cortical representations, in which the expansion correlates with the individual gain [8, 32]. We have shown that the individual perceptual improvement in the finger tips prompted by short periods of tactile coactivation (a repetitive, high-frequency stimulation) correlated with changes in the cortical representations of the finger [13–15]. Similar findings were reported after 5 Hz transcranial magnetic stimulation [16]. More recently, it was demonstrated that even under baseline conditions, the size of cortical representations predict performance: in the human visual system, Vernier acuity is related to cortical magnification in the primary visual cortex (i.e., V1) [33]. For the somatosensory cortex, tactile hyperacuity was shown to be largely determined by the cortical representation of the fingers in SI [34]. With the use of adult mice genetically engineered to overexpress the transcription factor EMX2 in embryonic cortical progenitor cells, it was demonstrated that cortical area size dictates performance at modality-specific behaviors [35].

However, there are exceptions to the rule that large maps always go with high-level performance, implying that the relation between behavior and cortical map might be more complex. In deprived animals, the amount of active exploration appeared to determine the direction of plastic changes [11]. In musicians, cortical activation during music performance has been found to be more focused, a phenomenon that was linked to automatization of highly trained musical sequences [36, 37]. During development of implicit knowledge, both in the motor and the perceptual domain, there is evidence of a complex time course of plastic changes, in which cortical maps become progressively larger during initial learning. Later representations return to their original topography, whereas the improvement of performance remains unchanged [3, 38]. More recently, abnormal map expansion of the SI hand representation has been reported to develop with impaired tactile acuity in elderly participants, a finding attributed to disintegration of cortical maps due to reduced intracortical inhibition developing with age [39].

In the present study, we show that reduced use also has an impact on cortical activation. In contrast to the typical enlargement of cortical maps after enhanced use, two weeks of immobilizing the index finger resulted in a significantly reduced hemodynamic response in the SI representation. These findings are in line with the shrinkage reported in the human motor cortex after leg immobilization [21] and with animal studies summarized above. Thus, our findings extend the theory of use-dependent plasticity as a determinant of brain organization by showing that reduced use induced by two weeks of immobilization reversibly affects perception in a maladaptive way in parallel with cortical reorganization.

In addition to maladaptive changes, we also observed increased frequency of hand use and improved tactile acuity, presumably reflecting compensatory processes. Enhanced discrimination abilities in blind Braille readers can be explained by the unusual and extensive use of the fingers for gathering fine-scale spatial tactile information [2, 40]. Similarly, spatial tactile acuity in professional pianists is significantly higher as compared to a nonmusician control group [41], although piano playing per se has little to do with the aspect of tactile acuity beyond the fact that professional playing requires extreme usage of the fingers. More recently, tai chi practitioners have been shown to have better tactile acuity, although this is largely unrelated to finger usage [42]. In the context of our study, it is important that an intensive practicing routine alters the input statistics for the fingertips. As a result, synaptic efficacy is modified, which in turn drives cortical reorganization. All of these changes then alter the way in which sensory information is processed in the somatosensory cortex, leading to, among other things, a lowering of spatial discrimination thresholds [43, 44].

Forms of perceptual compensation, possibly through modulation of interhemispheric interactions, have been described during acute hand deafferentiation [28, 45]. In our experiments, retesting two weeks after cast removal showed that the superior tactile performance of the unaffected, healthy finger persisted, which could be due to perceptual learning and its consolidation that occurred during the weeks of immobilization or to a continuation of enhanced use of the unaffected hand. According to the studies on transient deafferentiation ([28and 45]; see also [46]), interhemispheric interactions that are inhibitory in nature affect both the motor and the somatosensory cortex. Thus, as the cast patients used their unaffected hands more frequently, it is possible that the activation in the hemisphere representing the non-cast-wearing hand was enhanced, which may induce an increased interhemispheric inhibition targeting the somatosensory cortex of the cast hand, resulting in decreased BOLD activation and impaired behavioral performance. Alternatively, a more

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parsimonious explanation could be that the altered frequency of use in both the immobilized and the healthy hand led to lower activation in the brain region corresponding to the immobilized side and to increased activation in the brain region corresponding to the healthy side. Additional experiments, in which the frequency of use of the healthy and the immobilized hand are titrated, are needed for insight into contributing mechanisms.

What are the functional consequences of immobilization-induced perceptual and cortical impairment? Even brief periods of reduced use of a body part have overt, measurable consequences, and thus must be regarded as a significant driving force of brain organization equivalent to enhancement of use. According to our data, whatever one is doing or not doing leaves measurable traces in brain organization, either beneficial or harmful. Doing nothing does have negative consequences, suggesting that a continuous stream of sensory input may be necessary for maintaining intact brain organization and perceptual abilities.

Experimental Procedures

Subjects

We tested 31 cast-wearing subjects (38.4 ± 18.0 yrs [mean ± SD], range: 17–78 yrs) and 36 healthy, age-matched controls (40.0 ± 14.7 years, range: 17–78 years). All were right-handed according to the Oldfield questionnaire for the assessment of handedness. Cast-wearing subjects wore a unilateral plaster cast (13 on their left hand and arm, 18 on their right) for stabilization of the hand after bone fractures in the forearm or hand. Mean total duration of cast wearing was 5.8 ± 2.2 wks (range: 4–10 weeks), and duration of cast wearing at time of testing was 22.6 ± 10.2 days. fMRI measurements were performed on two subpopulations of 12 (four and eight) subjects in total. Cast subjects were neurologically healthy, per clinical examination by a neurologist and a pain specialist; none of them experienced sustained pain during or after wearing a cast. Individuals with peripheral nerve lesions, polyneuropathy, or neuropsychiatric diseases or signs of a CRPS were excluded. None of the subjects were taking centrally acting medication. All subjects gave their written informed consent before participating. The study was approved by the Ethics Committee of the Ruhr University of Bochum and was performed in accordance with the 1964 Declaration of Helsinki.

Assessment of Frequency of Arm Use through Acceleration Measurements

To obtain an objective measure of reduced use, we recorded arm movements in cast-wearing subjects during the immobilization period (n = 15) and in the control group (n = 10) by using ActiTrac monitors (IM Systems) containing a ceramic biaxial piezoelectric accelerometer sensor that records motion in two planes (vertical and front-to-back axes). The devices were fixed on the wrists of both hands for 2–4 hr (duration 3.23 ± 0.82 hr; mean ± SD). As a rule, ActiTracs were used at the subjects' homes, but in some cases they were used also at the hospital. Subjects had been instructed not to watch television or to take walks but to engage in activities of daily living requiring the use of both hands and arms. The ActiTrac monitors digitized the acceleration signals every 2 s, resulting in 30 epochs per min in units of mG (sensitivity 1.25 mG). The data were stored for offline analysis. Epochs for the right and left wrist-movement activity were compared with the use of the Student's paired t test.

Measurement of Two-Point Discrimination Thresholds

Tactile spatial two-point discrimination thresholds of the tip of the index fingers were assessed with the method of constant stimuli. We used seven pairs of needles (diameter 200 μm) with separation distances of 1.0, 1.4, 1.8, 2.2, 2.6, 3.2, and 4.0 mm. In addition, zero distance was tested with a single needle. After each presentation subjects had to immediately decide whether they had the sensation of one or two tips by answering "one" or "two." No feedback was given. Each distance of the needles was tested seven times in randomized order. The summed responses were plotted against tip distance as a psychometric function for absolute threshold, fitted by a binary logistic regression (SPSS). The threshold value was obtained from the fit at the distance where 50% correct responses was reached. A stable baseline of performance was accomplished through testing subjects in four consecutive sessions on one index finger. Averaging of sessions 1– 4 determined thresholds. According to repeated-measures ANOVA, all participants achieved a stable performance during the initial sessions 1–4.

fMRI Measurements

fMRI measurement was performed in block design with a whole-body 1.5 T scanner (Magnetom Symphony, Siemens Medical Systems, Germany) equipped with a high-power gradient-system (30 mT/m/s; SR 125 T/m/s), using a standard imaging head coil. BOLD images were obtained with a single-shot SpinEcho-EPI sequence (TR 3000 ms, TE 60 ms, matrix 64×64, field of view [FOV] 224 mm, 5 mm slice thickness, 1 mm gap between slices, voxel size 3.5×3.5×4 mm). We acquired 16 transaxial slices, parallel to the AC-PC line, covering the whole brain. For finger stimulation, we used electric stimulators (TENS stimulator, Medicommerz, Kirchzarten, Germany; DIGITIMER DS7A, Digitimer, England) with ring electrodes mounted on the tip of the index finger (pulse duration 0.1 ms, repetition rate 3 Hz). Stimulation intensity was adjusted to 1.5× above sensory threshold. We performed fMRI scanning by using 13 rest blocks without electrical stimulation and 12 blocks of stimulation, each of which contained 20 scans, resulting in a total number of 510 scans. Patients were instructed to keep their eyes closed and to concentrate on stimulation during the whole session. Anatomical images were acquired with an isotropic T1-3 dGE (MPRAGE) sequence (TR 1790 ms, TE 388 ms, matrix 256×256, FOV 256 mm, 1 mm slice thickness, no gap, voxel size 1×1×1 mm) with 160 sagittally orientated slices covering the whole brain. Imaging data were analyzed with the Statistical Parametric Mapping (SPM) software package, versions 99 and 5 (UCL Wellcome Trust Centre for Neuroimaging, London, UK), running under the MATLAB R12 environment (Mathworks, Sherborn, MA). The first ten images of each fMRI session, during which the BOLD signal reaches steady state, were discarded from further analysis. Single-subject spatial preprocessing consisted of realignment of all images to the first volume, generation of a mean image that corrected for head movement artifacts, normalization into standard stereotaxic space at 2×2×2 mm with an EPI template provided by the Montreal Neurological Institute, and smoothing with a 6 mm (full-width half maximum) isotropic, three-dimensional Gaussian filter. In single-subject analyses, contrast images comparing activation during sensory stimulation to the rest phases were calculated for both scanning sessions (with and without cast). The resulting contrast images were then entered into a random-effects analysis for evaluation of pre and post differences. Using paired t tests, we compared the activation patterns during cast wearing and after cast removal (extent threshold $k = 20$ voxels; height threshold $t = 1.89$, $p < 0.005$ uncorrected). For further quantification, for each subject the pre- and post-BOLD mean signal intensity in SI during stimulation was extracted from a cluster-sized region of interest built from the activated SI cluster.

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