

Rapid Experience-Dependent Plasticity following Somatosensory Damage

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Summary

Studies in nonhuman primates have provided evidence of rapid neural reorganization in somatosensory cortex after brain damage [1] and amputation [2]. Furthermore, there is also evidence of experience-dependent plasticity in both human [3–5] and nonhuman primates [6] that is induced by repetitive tactile stimulation. Given the evidence of plasticity subsequent to both neural damage and tactile experience, we hypothesized that somatosensory damage could lead to increased levels of experience-dependent tactile plasticity. To examine this hypothesis, the tactile localization judgments of two individuals with left hemisphere somatosensory damage subsequent to stroke were examined. Suprathreshold tactile stimuli were presented to the hand or forearm, and the effect of the location of previous stimulation on localization judgments for subsequent stimuli was examined. Results showed that, only on the contralesional limb, even a single tactile stimulation could induce a significant perceptual shift in localization judgments for subsequent stimuli, with shifts occurring in the direction of the preceding stimulation. These results provide novel evidence of a very rapid time course for substantive perceptual changes in tactile location perception in response to simple stimulation, revealing a highly plastic and dynamic tactile system even many years after neural damage.

Results

Experiment 1—Evaluating Experience-Dependent Effects on Tactile Localization Judgments

Two individuals with left hemisphere somatosensory damage (RSB and DLE) and 12 older controls (mean age: 71.8 years; range: 65–84 years) were instructed to localize all tactile stimuli presented in three different conditions: hand only, hand/forearm, and forearm only. In the hand-only and forearm-only conditions, all stimuli were presented on the same body part (hand or forearm). In the mixed hand/forearm condition, each stimulus to the hand was preceded by zero, one, or three stimuli in different forearm locations. If stimulation can induce shifts in location perception, then the perceived location of hand stimuli should be affected by the prior presentation of forearm stimuli. Specifically, proximal shifts in location perception for hand stimuli might be expected when they are preceded by forearm stimuli. For RSB, testing was carried out on the palmar surface of the contralesional and ipsilesional hands, with the ipsilesional hand providing a within-subject control condition to check if the participant could carry out the task and if the deficit and/or phenomena of interest were limited to the

contralesional limb. Due to hemiparesis, DLE was not able to use his contralesional hand to make localization judgments regarding his ipsilesional limb and reduced muscle tone in his contralesional hand made it difficult to keep his hand flat for palmar surface testing. For these reasons, stimuli were presented only to the dorsal surface of DLE's contralesional hand. Control participants were tested on the right palmar surface. For each condition, the average localization bias and error (signed and unsigned distance from the location of the tactile stimulus to the perceived location) was measured separately along the distal-proximal axis (parallel with the long axis of the fingers) and the radial-ulnar axis (perpendicular to the distal-proximal axis). Positive values indicate distal and radial bias and negative values indicate proximal and ulnar bias.

First, results from the hand-only condition indicated that, for both RSB and DLE, localization judgments on the contralesional hand were inaccurate (Figures 1A and 1C), exhibiting a proximal shift toward the center of the hand, consistent with previous findings [7]. This represents a “baseline” distortion in the perception of tactile stimulation to the hand that contrasts with controls who were significantly more accurate (mean distal-proximal error: controls, 0.34 cm; RSB, 2.59 cm; DLE, 3.31 cm; $p < 0.00001$).

Second, controls exhibited no significant shift in location perception between hand-only and hand/forearm conditions (+0.03 cm, $t(11) = 0.78$, $p = 0.45$). In contrast, RSB and DLE perceived contralesional hand stimulations to be even more proximal in the hand/forearm condition than in the hand-only condition (RSB, -2.0 cm; Figure 1B) and (DLE, -3.1 cm; Figure 1D). A Bayesian analysis comparing single cases to controls with baseline (hand-only) accuracy as a covariate [8] confirms that for both RSB ($p < 0.001$) and DLE ($p < 0.001$), the proximal shift was significantly greater than for controls. In addition, compared to controls, DLE exhibited a significant ulnar shift in the hand/forearm versus hand-only condition (-1.31 cm, $p = 0.031$), but not RSB (-0.16 cm, $p = 0.582$).

For RSB, the proximal shift in the hand/forearm versus hand-only conditions was significantly greater on the contralesional (-2.09 cm) versus ipsilesional (-0.11 cm) limb ($t(17) = 7.52$, $p < 0.00001$). Comparable shifts in the hand/forearm versus hand-only conditions were also found in two additional, similar experiments that did not require overt localization of forearm (wrist) stimulations (Supplemental Experimental Procedures, “Supplemental Experiment 1,” available online) and controlled for potential attentional confounds (Supplemental Experimental Procedures, “Supplemental Experiment 2”).

Third, this experiment allowed for the evaluation of whether the proximal shift was driven by *immediately* preceding stimulations. Controls demonstrated nonsignificant differences between conditions with different numbers of preceding forearm stimulations ($p = 0.135$, repeated-measures ANOVA). In contrast, both RSB and DLE exhibited significantly larger proximal shifts on trials with one or three versus zero immediately preceding forearm stimulations (see Figure 2). DLE (but not RSB) also exhibited greater proximal shift with three versus one preceding forearm stimulations; this greater lability could perhaps be due to his more extensive lesion. These results reveal that it is not the presence of many forearm stimulations within a block of trials that induces a perceptual shift

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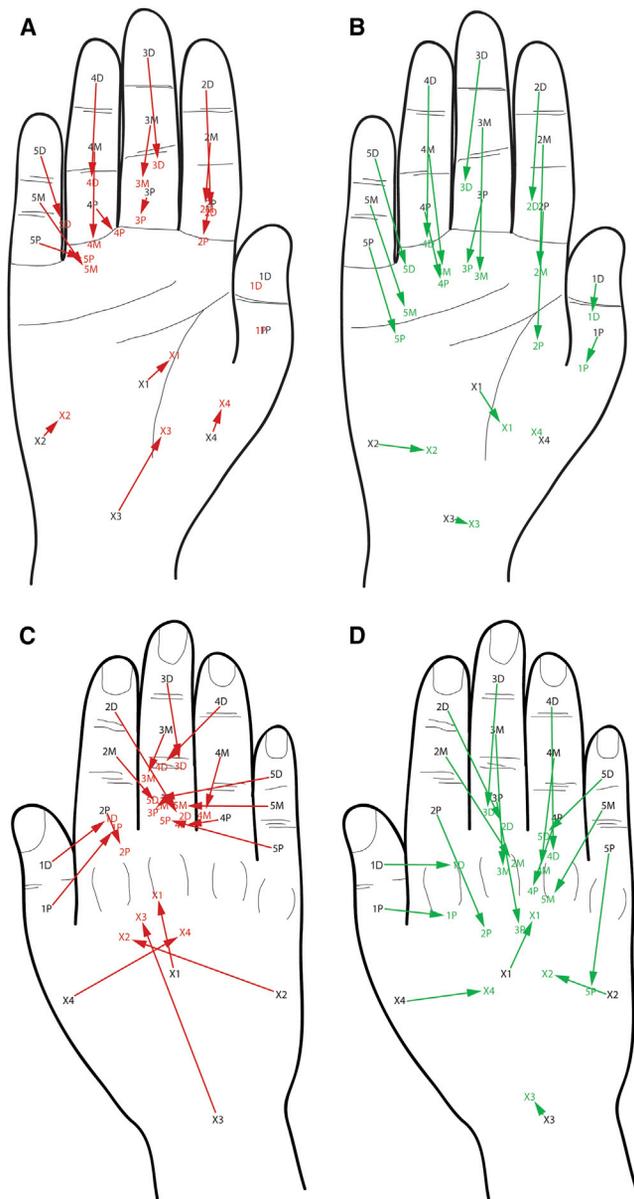


Figure 1. Tactile Localization with or without Prior Forearm Stimulation
The 18 stimulation points on the hand in experiment 1 are shown in black. Mean localization judgments for each stimulation point for RSB (A and B) and DLE (C and D) are shown. Red (A and C) indicates the mean localization judgments in the hand-only condition, with green (B and D) indicating mean localization judgments in the hand/forearm condition. Arrows visualize the distance and direction of the shift in localization judgments from the stimulation point to the mean localization judgment. See also [Figure S1](#).

but that a single stimulation may have substantive perceptual consequences. In sum, these findings reveal clear, rapid, experience-dependent changes in location perception.

Experiment 2— Proximal/Distal Perceptual Shifts Relative to a Constant Target Location

This experiment examined whether the shifts observed in experiment 1 and supplemental experiments 1 and 2 simply reflected an accentuation of baseline localization biases or were specifically driven by the location of stimulations within a recent time window. To test this, on each trial, a tactile

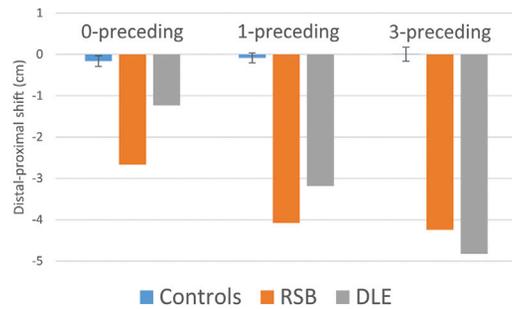


Figure 2. Shift in Localization Judgments by Number of Preceding Forearm Stimuli

In experiment 2, mean distal-proximal shift (proximal = negative) in localization bias (in cm) from the hand-only versus the hand/forearm conditions, according to the number of preceding forearm stimuli, for controls (error bars indicate 95% confidence interval), RSB, and DLE. Compared to controls, both RSB and DLE exhibited significant differences in the extent of proximal shift between hand stimulation trials with zero versus one preceding forearm stimulations (RSB: $t(11) = -4.67, p = 0.0007$; DLE: $t(11) = -6.37, p = 0.00005$), for zero versus three (RSB: $t(11) = -6.42, p = 0.00005$; DLE: $t(11) = -13.8, p < 0.00001$) and for three versus one preceding forearm stimulations for DLE only (RSB: $t(11) = -1.02, p = 0.327$; DLE: $t(11) = -6.64, p = 0.00004$). Neither controls nor RSB or DLE demonstrated significant differences among any of the three conditions along the radial-ulnar dimension.

stimulation was delivered to the middle segment of one of the four fingers on the contralesional hand, preceded by a “prime” stimulation to either the distal or proximal segment of the same finger. Participants reported only the location of the second stimulation. The experience-dependent plasticity hypothesis predicts that localization judgments should shift in the direction of the prime stimulation.

Control participants demonstrated no significant difference in localization judgments for distal (-0.48 cm) compared to proximal (-0.37 cm) primes ($t(11) = 1.16, p = 0.269$). In contrast, RSB and DLE’s localization judgments were modulated by the location of the prime stimulations. Proximal priming resulted in an average shift of -4.17 cm for RSB and +1.29 for DLE and distal priming in an average shift of -3.44 cm for RSB and +2.20 for DLE. DLE exhibited an overall distal shift in localization perception in this experiment compared to experiment 1. This may simply reflect general experience-dependent changes, because testing occurred several months after experiment 1 (see [9, 10] for similar long-term shifts in referred sensation of amputees). Critically, however, as predicted by the experience-dependent plasticity hypothesis, the difference between proximal and distal priming conditions (RSB, +0.73 cm; DLE, +0.91 cm) was significant for both RSB and DLE compared to controls ($t(11) = 2.42, p = 0.034$ and $t(11) = 2.94, p = 0.013$). These findings revealed that, rather than simply accentuating baseline biases, preceding proximal and distal stimulations shifted subsequent localization judgments in their respective directions.

Discussion

Experiments with two individuals with left somatosensory damage revealed that their perceptions of the locations of tactile stimulations presented to the contralesional hand were significantly influenced by the locations of preceding stimulations. These findings provide the first report of very rapid, experience-dependent perceptual plasticity in response to brief tactile stimulation. In experiment 1, the perception of

stimuli presented to the fingers was shifted proximally when the stimuli were preceded by even a single stimulation to the forearm. Experiment 2 showed that the shifts observed in experiment 1 were not simply an accentuation of baseline biases, but that perception shifted either proximally or distally depending on the location of a preceding stimulus, thus confirming the experience-dependent nature of the phenomenon. Further, an alternative explanation that attributes the findings to attentional or other biases that shift perception toward the center of a changing response or stimulation space [11] is unlikely given that perceptual shifts influenced by prior stimulation were observed when the response space was unchanged (Supplemental Experimental Procedures, “Supplemental Experiment 1”), responses were not biased to the center of the stimulus space in blocks with stimuli presented to the fingers only (Supplemental Experimental Procedures, “Supplemental Experiment 1”), and attentional manipulations do not influence the observed shift (Supplemental Experimental Procedures, “Supplemental Experiment 2”).

The fact that both participants had intact tactile *detection* of suprathreshold stimuli, despite substantial damage to the hand area of S1, indicates that cortical reorganization had taken place. That this reorganization was not completely successful is evidenced by the following: (1) the “baseline” distortions in tactile location perception exhibited by both participants and (2) the rapid, experience-dependent perceptual shifts. The first [7] presumably reflects changes in somatosensory maps given the reduced representational space resulting from the extensive damage suffered. These baseline perception shifts would be expected if higher-order body representations that receive their input from these maps [12, 13] were not able to generate a correct perception of the actual stimulation locations. Our focus here, however, is on the phenomenon of rapid, experience-dependent perceptual changes.

The finding of rapid perceptual changes, several years after neural injury, provides a window into the processes by which tactile map boundaries and receptive fields are defined and redefined. Presumably, these same mechanisms support experience-dependent plasticity in neurologically intact individuals, with neural injury simply exposing them more clearly. Various computational models [14–17] have proposed mechanisms to account for the reported plasticity of somatosensory maps due to amputation, intense practice, or neural damage. Key concepts from these proposals are (1) *divergent arborization* from lower levels (e.g., thalamic) to somatosensory maps provides broader neuronal connectivity than is apparent when the stable system is evaluated by standard electrophysiological techniques that reveal narrowly tuned receptive fields, (2) *functional sharpening* of this broad neuroanatomical connectivity produces well-defined boundaries through competitive processes in which inhibition plays a key role, (3) *experience-dependent synaptic processes* allow for neuronal competition to yield dynamic map boundaries that are shaped by experience, and (4) *population coding* entails that perceptual experience is determined by the integration of the activations across the broad set of active neurons. Below, we provide a brief sketch of the application of these principles to an account of the findings reported here, although computer simulation work would be critical for developing an appropriately detailed account.

In neurologically intact individuals, improvements in tactile acuity have been observed after only 2–3 hr of tactile coactivation training on a single finger [4] along with concomitant changes in the finger representation in S1 [18, 19]; similarly,

an increase in tactile localization errors has been observed after 3 hr of multifinger coactivation stimulation [20–22]. The extreme lability we have reported here subsequent to brain damage may be the result of the reduced representational space of the reorganized maps and/or the disruption of inhibitory processes that normally develop and maintain well-defined map boundaries. In other words, normally divergent arborization in the context of decreased inhibition may allow for somatosensory maps to be more easily influenced by temporally local stimulation patterns, producing the observed rapid changes in cortical map topography. With regard to the role of inhibition reduction, there is evidence for decreased cortical inhibition [23–25] even in the chronic (>6 months) post-stroke period in humans [26, 27].

In neurologically intact individuals who experience intensive discriminative somatosensory experience (e.g., violinists and musicians [28, 29]), higher-order body representations likely adjust to lower level somatosensory map changes. More dynamic perceptions after brain damage may be due either to an inability of higher-order representations to adjust to rapid changes in lower-level maps and/or to damage to the higher-order somatosensory or multisensory representations, a possibility that we cannot rule out in the cases reported here.

The high degree of plasticity observed several years after neural injury reveals the persistently dynamic nature of neural representations. On the positive side, this plasticity may potentially be harnessed in rehabilitation to improve function. However, hyperlabile systems such as the ones observed here may make it difficult to develop consistent and stable mappings from reorganized somatosensory maps to the higher-order body representations responsible for perceptual experience. Achieving an appropriate balance between plasticity and stability is critical for systems to adapt optimally to damage and disruption. As research directed at maximizing plasticity and reopening critical periods continues to make strides, advances in understanding the triggers and brakes on plasticity [30] will be critical for developing interventions that take advantage of the dynamic processes that may be present subsequent to neural injury.

Experimental Procedures

Case Report

RSB, a 61-year-old male reported on previously in [7], suffered a stroke 6 years prior to this investigation. This resulted in a left parietal lesion extending from the post-central gyrus to the angular gyrus, including the hand area of the primary somatosensory cortex (Figure S2A). DLE, a 74-year-old male reported on previously in [31], suffered a stroke 4 years prior to this investigation that resulted in a left frontoparietal lesion affecting most of the primary somatosensory cortex (Figure S2B). Both individuals could accurately use their ipsilesional left hands to point to locations in space and their own body parts with their eyes open. Both individuals demonstrated 100% accuracy for simple detection of suprathreshold stimuli presented to the hand and forearm areas.

General Methods and Data Analysis

In every experiment, stimulation consisted of a touch (approximately 6 g of force) applied with a flat rubber cylinder (5 mm in diameter) presented with the participant’s eyes closed. Immediately after stimulation, the participant was cued to open his eyes and immediately indicate the stimulation site by touching the location with the index finger of the opposite hand. Localization judgments were recorded by the experimenter on a line drawing of the subjects’ own hands. Online experimenter scoring for a subset of trials in experiment 1 (200 trials) were compared to video-based scoring to ensure accurate coding (average absolute difference between coding schemes = 0.2 cm). All within-subject analyses were two-tailed t tests comparing mean localization bias along each axis for each stimulation point.

Comparisons of single cases to controls utilized Crawford and Garthwaite's modified t test [32], unless otherwise noted. All research was approved by the institutional review boards of the University of Delaware and Johns Hopkins University.

Experiment 1

In the hand-only condition, on each trial, a stimulus was randomly presented to 1 of 22 points on the hand (Figure 1). In the forearm-only condition, stimuli were randomly presented to one of 24 points covering the length of the forearm (an 8 × 3 grid with points spaced 3.2 × 3.2 cm from each other). In the mixed hand/forearm condition, stimuli were presented to any of the 22 hand or 24 forearm locations. Stimuli in the hand/forearm condition were balanced such that 18 of the 22 hand-stimulation points were preceded equally by zero, one, or three forearm stimuli presented in different locations. Four locations at the base of the fingers were always preceded by a hand stimulus and not subsequently analyzed. Each testing session consisted of one block of trials for each condition, with block order counterbalanced across six sessions for DLE and RSB. Controls were tested for one session.

Experiment 2

Two stimulations were administered on each trial and participants were instructed to report the location of the second one. The first "prime" stimulation was applied to the center of the distal or proximal segment of one of the four fingers (excluding the thumb), followed approximately 1 s later by stimulation of the middle segment of the same finger. Each block consisted of 16 trials presented in random order, with stimulated finger and prime stimulus position (distal, proximal) balanced across trials. RSB (four blocks) and DLE (two blocks) were tested on the contralesional hand only, whereas controls were tested on the right hand (two blocks).

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures and two figures and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2014.01.070>.

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