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RESEARCH ARTICLE

Quantitative assessment of cortical somatosensory digit representations after median and ulnar nerve injury in rats

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Abstract

Incomplete recovery of sensory function is common after peripheral nerve injury (PNI). Despite reinnervation following injury, disorganized cortical representations persist and may contribute to functional deficits. There is a dearth of literature characterizing cortical responses after PNI in rodent models. Here we develop a quantitative electrophysiological method for mapping forepaw digit responses in primary somatosensory cortex (S1) of rats. We tested the hypothesis that PNI in the forelimb would generate significant, long lasting sensory deficits, and corresponding disorganization in S1. Rats underwent a transection of the proximal segment of the median and ulnar nerves in the forelimb followed by tubular repair. 4–12 months after nerve injury, we tested mechanosensory withdrawal thresholds and mapped S1 responses to mechanical stimulation of the digits. PNI produces persistent elevation of mechanical withdrawal thresholds, consistent with an impairment in sensory function. Assessment of cortical neurophysiology reveals a substantial disorganization of S1 somatotopy. Additionally, we document degraded timing and digit specificity of cortical responses. This quantitative measurement of long-term changes in S1 digit representations after forelimb nerve injury in rodents provides a framework for further studies focused on the development of therapeutic strategies to restore cortical and sensory function.

Keywords Peripheral nerve injury · Forelimb · Primary somatosensory cortex · Electrophysiology · Somatotopy

Introduction

Peripheral nerve injuries (PNI) significantly impact quality of life for millions of Americans and result in approximately $150 billion in annual health-care spending (Grinsell and Keating 2014). Surgical repair of damaged nerves allows restoration of connectivity after nerve transections, but more than half of patients have residual dysfunction following reinnervation (Lundborg 2003; Lundborg et al. 2004; Kouyoumdjian 2006; Grinsell and Keating 2014). Peripheral injuries induce changes throughout the nervous system as central networks adjust to changing afferent inputs (Navarro et al. 2007; Knox et al. 2015). Understanding central changes after nerve repair may guide therapy development and improve clinical prognoses.

In rodents, PNI causes persistent motor and sensory behavioral deficits (Bertelli and Mira 1993; Bontioti et al. 2003; Papalia et al. 2003, 2006; Bertelli et al. 2004, 2005; Galtrey and Fawcett 2007; Navarro 2016; Kemp et al. 2017). In concordance with these behavioral changes, crush injuries of peripheral nerves in the hind limb induce disruptions of cortical somatotopy (Barbay et al. 1999, 2002). While the majority of clinical incidence of traumatic PNI affects nerves in the upper limb, preclinical studies in rats have primarily focused on hind limb injury models and cortical electrophysiology has primarily been used as a gross indicator of reinnervation after forelimb injuries (Kouyoumdjian 2006; Wang et al. 2008). A clear and quantitative description of central nervous system dysfunction after forelimb

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nerve injury in rodents may be useful for developing new therapeutic strategies.

Here, we develop an electrophysiological method for mapping cortical responses to mechanical stimulation of the forepaw digits after nerve injury. We use quantitative measures of cortical organization and digit response specificity to test the hypothesis that severe PNI causes significant, long lasting deficits in S1 that accompany mechanosensory deficits. This quantitative electrophysiological approach to measure central organization after injury provides a basis for integrating central measures in assessing PNI outcomes in rats.

Materials and methods

Subjects

Twenty adult female Sprague–Dawley rats were used in this experiment. All handling, housing, and surgical procedures were approved by the University of Texas Institutional Animal Care and Use Committee. Rats were housed in a 12:12 h reversed light cycle environment with ad libitum access to food and water.

Median and ulnar nerve transection and repair

Lesions to the median and ulnar nerves in the right forelimb were performed as previously described (Meyers et al. 2017). Rats were anesthetized with ketamine hydrochloride (80 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.), and a small incision was made 1 cm proximal to the elbow on the medial surface of the right forelimb. The pectoralis muscle was retracted to expose the median and ulnar nerves, and both nerves were fully transected. The proximal and distal stumps of each nerve were sutured 1 mm inside the opposite ends of an 8-mm saline-filled polyurethane tube (Micro-Renathane, 0.095-in. outside diameter, 0.066-in. inside diameter; Braintree Scientific, Inc.; Braintree, Massachusetts), resulting in a 6-mm gap between nerve stumps. The skin incision was sutured and treated with antibiotic ointment. All rats were given Baytril (7.5 mg/kg) and sustained-release Buprenorphine (1.2 mg/kg) for 6 days following injury. All rats were placed in Elizabethan collars for 5 days following injury to prevent autophagia.

Forepaw sensory withdrawal threshold testing

Mechanosensory withdrawal threshold was assessed in all rats after PNI and in a subset of uninjured rats. Testing was performed in an acrylic chamber with a wire mesh floor. Forepaw touch sensitivity was tested using a dynamic plantar aesthesiometer (Ugo Basile; Gemonio, Italy). The actuator filament was applied to the plantar surface of the forepaw and a linearly increasing force was applied (20 s ramp time, 50 g maximal force). The force at which the forepaw withdrawal occurred was recorded for analysis. Left and right paws were alternately tested with a minimum of 1-min interval between consecutive tests. The average of five trials was used to determine the withdrawal threshold of each rat.

S1 recording and mechanical digit stimulation

Similar to previous procedures, rats were anesthetized with ketamine hydrochloride (75 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.), and mounted into a stereotaxic frame (Corbo et al. 2018). Supplemental doses were administered as necessary to maintain a stable plane of anesthesia monitored by toe pinch reflex. To prevent cerebral edema, a cisternal drain was performed. A craniotomy and durotomy exposed left S1, which was covered with silicone oil to prevent drying. The right forepaw was glued in a natural position to a podium with a nearly vertical plane, exposing the glabrous side of the paw and providing access to digits 2–5. Mechanical tactile stimulation was delivered by custom-built electromagnetic devices (Fig. 1; parts acquired from McMaster-Carr, Douglasville, GA). Brief (5 ms) pulses of DC current engaged the electromagnet (Cat# 69905K173) to move the stimulator shaft (Cat# 6112K34) forward. A shaft collar (Cat# 57485K64) constrained by the device housing restricted the movement to 500 µm. A compression spring (Cat# 9657K43) returned the shaft to its resting state, and a linear bearing (Cat# 61205K72) ensured a consistent motion. The device housing was custom designed with CAD software and 3D printed. A 3D-printed cylindrical tip tapered to a 2-mm diameter was positioned orthogonally to the digit and adjusted under a binocular microscope to deliver a just noticeable indentation to the distal end of the digit. An identical device was positioned over each digit to deliver consistent, interleaved stimulation of digits 2–5. One rat was excluded from analysis due to poor stimulator positioning during the experiment.

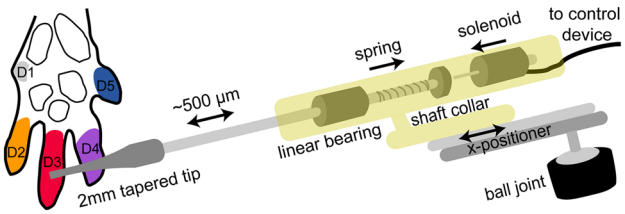

Fig. 1 Design of tactile stimulation device. Illustration of design for electromagnetic stimulators. Four identical devices were carefully positioned over each digit to deliver interleaved stimulation of D2–5. Devices were controlled by neural recording software to deliver consistent mechanical stimulation during recordings. Paw and stimulator are not illustrated to scale

An image of the cortical surface was captured with a calibrated microscope camera, and each electrode penetration site was digitally recorded with reference to cortical surface vasculature. A pair of parylene-coated tungsten microelectrodes spaced at 240 µm (1–3.5 MΩ, FHC) was used to record S1 responses. The electrode pair was progressively placed at recording sites approximately evenly spaced throughout the digit region of S1 while avoiding blood vessels. Electrodes were lowered to approximately 650 µm below the pial surface to record multiunit spiking activity in layer IV of the cortex. At each recording site, individual mechanical tactile stimulation of digits 2–5 was delivered 20 times at 2 Hz in a randomly interleaved order using the electromagnetic devices described above. Neural signals were differentially amplified using an RA16PA preamplifier (Tucker-Davis Technologies, Alachua, FL) from a common reference and ground attached to the neck muscles. Signals were digitized at 24.414 ks/s with 16-bit resolution and bandpass filtered from 300 to 3000 Hz using an RZ5 BioAmp processor (Tucker-Davis Technologies). Multiunit spike data were recorded and monitored online with Brainware software and binned at 1 ms for 100 ms preceding and 350 ms following the onset of each tactile stimulus. Map borders were established by traditional methods of receptive field definition by monitoring neural activity in response to manual stimulation with a hand-held probe (Chapin and Lin 1984; Waters et al. 1995; Xerri et al. 1996). The contiguous digit region was mapped completely and was constrained by recording sites with lower lip, D1, thenar, palmar, or hypothenar pad receptive fields, or by sites with no discernable receptive fields.

Neurophysiology data analysis

The preferred digit at each recording site was determined by the maximal number of driven spikes in response to individual digit stimulation. Response periods were defined for each stimulation type from an average PSTH. Onset latency was defined as the first bin after tactile stimulation with a z score > 2. End of response latency was defined as the bin prior to the next three contiguous bins where $z < 2$. Driven spikes for each stimulation type were defined as the driven spike rate (mean response period–mean spontaneous period [1–90 ms]) × response duration (end of response latency − onset latency).

Digit response specificity was determined by Bonferroni-corrected paired t tests on the number of driven spikes in response to stimulation of each digit. Digit specificity was defined as four minus the number of digits driving significantly fewer spikes than the preferred digit. Voronoi tessellations were made using the coordinates of each recording site to determine their representative area (Kilgard and Merzenich 1998; Engineer et al. 2011). The total digit area for each map was determined, and the percentage of cortex with each digit specificity was compared between groups.

The location and preferred digit of recording sites were used to analyze the somatotopic organization of each cortical map. Site locations were transformed in one degree increments in polar coordinates, and then flattened along the y dimension in Cartesian coordinates. Sites corresponding to digit 2–5 were numerically coded, and the coefficient of determination relative to their x-axis location was calculated. The maximum coefficient value was used as a measure of map somatotopy.

Statistics

Mean neurophysiological measures were determined from all digit sites for each rat and compared across experimental groups using t tests for individual samples. Cortical areas of digit response specificity and somatotopic organization measures were compared between groups using t tests for individual samples. All descriptive statistics for each group are reported as the mean ± standard error.

Results

Persistent elevation of tactile withdrawal thresholds following PNI

Ten rats underwent a transection of the right median and ulnar nerves followed by tubular repair with a 6-mm gap. 4–12 months later, mechanosensory withdrawal thresholds were tested. As expected, nerve injury tripled withdrawal thresholds in the injured right forelimb compared to the subset of uninjured controls (Fig. 2; UI subset ($N = 4$) = 10.2 ± 1.71, PNI ($N = 10$ on all following) = 27.79 ± 1.87; t test for individual samples, $p = 1.38 \times 10^{-4}$). This increase in withdrawal thresholds indicates a reduction in tactile sensation in the forepaw. As expected, no differences were observed in the uninjured left forelimb (Fig. 2; UI subset ($N = 4$) = 9.25 ± 0.89, PNI = 8.83 ± 0.53; t test for individual samples, $p = 0.68$).

Nerve injury degrades temporal dynamics of cortical responses to tactile stimulation

Multiunit recordings in response to mechanical stimulation of the digits were made across the contiguous digit region in left S1 in nine uninjured and in ten PNI rats 4–12 months after injury (Fig. S1). The total area of the digit region was similar between groups [UI ($N = 9$ on all following) = 1.63 ± 0.11 mm^2, PNI = 1.45 ± 0.12 mm^2; t test for individual samples, $p = 0.29$], and there were a similar number of recording sites per map (UI = 26.33 ± 1.35,

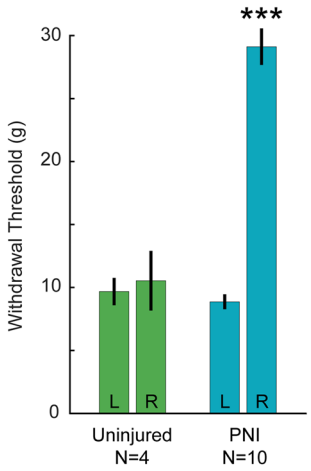

Fig. 2 Median and ulnar nerve injury results in lasting deficits in mechanosensory function. Forepaw withdrawal thresholds to mechanical stimulation of the injured (right) paw are significantly increased after PNI. No differences in withdrawal threshold are observed in the uninjured (left) paw. ***$p < 0.001$

PNI = 25 ± 2.16; *t* test for individual samples, $p = 0.62$). Cortical organization of digit representation in uninjured rats was in keeping with the well-known somatotopy (Chapin and Lin 1984; Waters et al. 1995; Xerri et al. 1996; Coq and Xerri 1998, 1999a; Xerri and Zennou-Azogui 2003; Zennou-Azogui et al. 2016). Consistent with studies in non-human primates, the digit region remained in the same relative stereotaxic location; and the region borders had similar compositions following nerve injury (Merzenich et al. 1983; Wall et al. 1986; Florence et al. 2001).

To assess deficits in sensory evoked responses, cortical activity in response to preferred digit stimulation was compared between PNI and uninjured rats. In uninjured rats, D2–4 representations accounted for similar areas of the digit region, while D5 areas were smaller (Fig. S2). This was consistent after PNI, while some rats did not have any D5 preferred sites (Figs. S1 and S3). All timing measures documented slowed cortical responses. The response onset to tactile stimulation was significantly slower following nerve injury (Fig. 3b; UI = 13.71 ± 0.27 ms, PNI = 15.71 ± 0.71 ms; *t* test for individual samples, $p = 0.022$). The latency from onset to peak was also extended (Fig. 3c; UI = 3.08 ± 0.19 ms, PNI = 4.42 ± 0.36 ms, *t* test for individual samples, $p = 0.006$). The duration of cortical responses was also extended after PNI (Fig. 3d; uninjured = 12.34 ± 1.04 ms, PNI = 17.91 ± 1.74 ms; *t* test for individual samples, $p = 0.016$). Measures of response strength were similar following PNI. The strength of the peak cortical response was similar after PNI (maximum spikes per 1 ms bin, UI = 0.65 ± 0.04, PNI = 0.61 ± 0.03; *t* test for individual samples, $p = 0.44$). Responses in the PNI group demonstrated a trend toward an increase in total driven spikes in response to stimulation, but the effect failed to reach

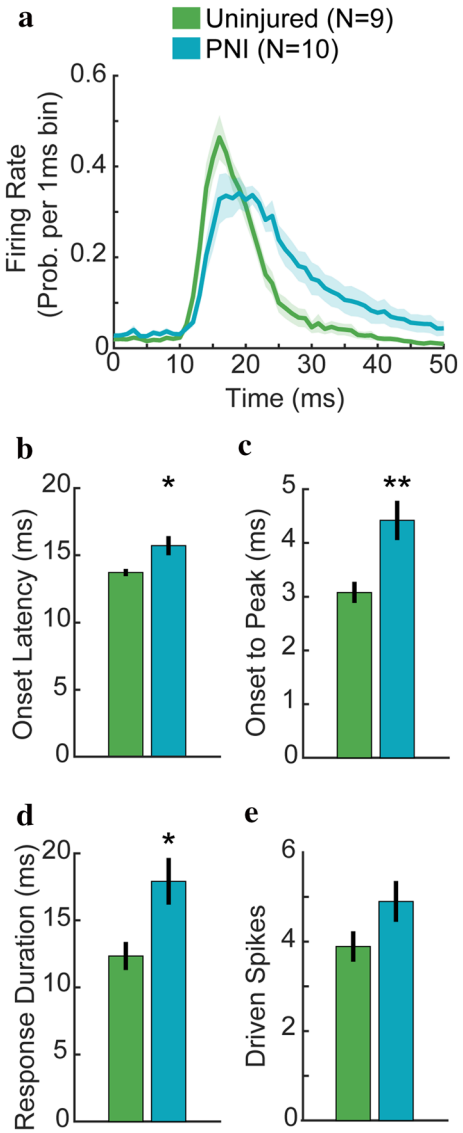

Fig. 3 Degraded cortical response timing to preferred digit stimulation after nerve injury. **a** Average PSTH of preferred digit responses. PNI causes slowing and broadening of responses to stimulation, as evidenced by a significant increase in onset latency (**b**), onset-to-peak duration (**c**), and response duration (**d**). A trend toward increased driven spikes was observed by failed to reach significance (**e**). *$p < 0.05$, **$p < 0.01$

significance (Fig. 3e; UI = 3.89 ± 0.34, PNI = 4.90 ± 0.46; *t* test for individual samples, $p = 0.10$). Together, these results suggest extensive reinnervation of mechanoreceptors, but persistent changes in cortical response patterns to sensory input.

Degraded digit specificity and somatotopic disorganization following nerve repair

Our electrophysiological recordings allow for quantitative characterization of digit responses at each recording site.

Thus, we next tested the specificity of cortical responses to tactile stimulation of each digit (Fig. 4a). In uninjured rats, nearly 40% of the digit cortex responded selectively to a single digit. PNI resulted in a substantial reduction in individual digit selectivity, with only 12% of cortex represented by individually selective sites (Fig. 4b; UI = 38.26 ± 5.8%, PNI = 11.77 ± 2.82%; *t* test for individual samples, $p = 5.48 \times 10^{-4}$). Three-digit responsive areas comprised the largest portion of digit cortex in PNI rats, a significantly larger area than observed in uninjured rats (Fig. 4b; UI = 15.78 ± 3.88%, PNI = 38.62 ± 4.55%; *t* test for individual samples, $p = 0.0015$). These results represent the first report of degraded forelimb digit response specificity in rodent S1 after peripheral nerve injury and repair, and reflects reorganization described in non-human primate studies (Wall et al. 1986; Florence et al. 2001).

To quantify cortical disorganization after nerve injury, we assessed somatotopy of the digit representations in S1 by calculating the best coefficient of determination for preferred digit response organization along a linear axis. A higher coefficient value indicates that the preferred digit sites tend to be clustered and sequentially organized across the digit region, while a lower value coefficient suggests interleaved and unpredictable localization (Fig. 5a). Maps of uninjured rats were highly organized, while PNI caused a substantial and significant degradation of somatotopic organization (Fig. 5b; UI = 0.81 ± 0.02; PNI = 0.28 ± 0.06; *t* test for individual samples, $p = 2.98 \times 10^{-7}$). This demonstrates large-scale reorganization of cortical representations resulting from disorganized reinnervation, highlighting the central changes that occur in response to peripheral nerve injury.

Discussion

Recovery of sensory function in the forelimb remains significantly diminished for many patients despite effective reinnervation after peripheral nerve injury (Jaquet et al. 2001; Lundborg and Rosén 2001). Changes in central organization arise following PNI and may contribute to the lasting changes in sensory function (Lundborg 2003; Navarro et al. 2007). Here, we document extensive cortical deficits accompanying behavioral impairments in sensory function following injury as measured by increased mechanosensory withdrawal thresholds. Using quantitative electrophysiological methods for comparing responses to mechanical digit stimulation across the extent of the digit region of S1, we report persistent changes in evoked response timing, cortical somatotopy, and digit response specificity. In conjunction with interventions that promote peripheral reinnervation, an understanding of central reorganization in sensory networks may provide a framework to develop complementary therapies to target restoration of central processing.

Extensive reinnervation of deafferented areas after nerve repair does not ensure recovery of function. Here, we report persistent mechanosensory deficits despite similar response strength to stimulation of the forepaw digits after PNI. Accompanying this increase in withdrawal thresholds, we observed slowed response onset and onset-to-peak latencies, as well as prolonged response durations to preferred digit stimulation following PNI. Spike timing in response to forelimb stimulation influences stimulation location discrimination on a single trial basis (Foffani 2004). Thus, the observed degradation of response timing after PNI may contribute to impaired sensory function. Afferent signals travel

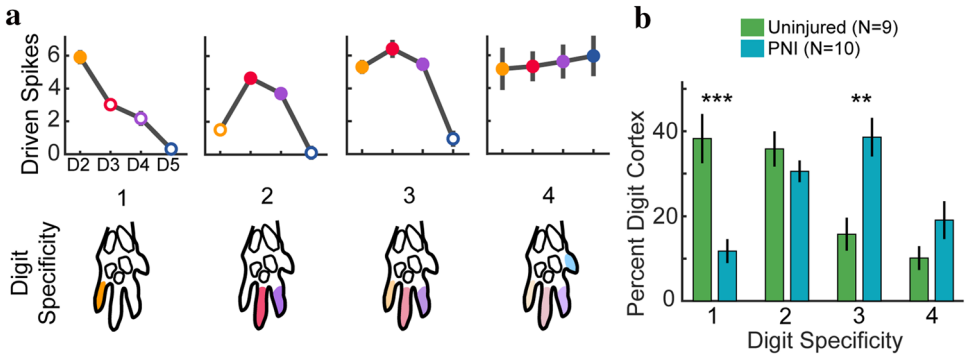

Fig. 4 Quantitative assessment of digit responses reveals reduction in specificity after nerve injury. **a** Representative data from sites with RF specificity to 1, 2, 3, or 4 digits. Open circles indicate responses that are significantly weaker compared to the preferred digit response (paired *t* test, Bonferroni corrected $p < 0.0167$). The left panel illustrates a site which demonstrated significantly reduced firing in response to stimulation of digits 3, 4, and 5 compared to digit 2 (the preferred digit), and thus was defined to have a digit specificity of 1. The right panel illustrates a site with no significant preference for any digit, and thus was defined to have a RF specificity of 4. **b** Average cortical area representing each level of specificity. PNI results in degraded response specificity, with a significant reduction in the area that preferentially responds to stimulation of a single digit and an increase in the area that responds to three digits. $^{**}p < 0.01$, $^{***}p < 0.001$

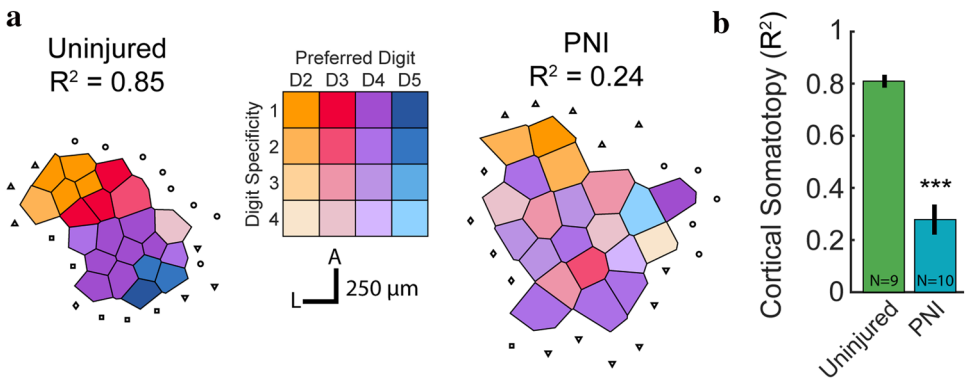

Fig. 5 PNI produces persistent somatotopic disorganization. **a** Representative S1 maps of an uninjured and a PNI rat. Preferred digit responses within the digit region of S1 are indicated by color for D2 (orange), D3 (red), D4 (purple), and D5 (blue) sites as determined by neural recordings. Color saturation decreases with decreased response specificity. Digit region borders are comprised of D1 or thenar (upward triangle), pad (circle), hypothenar (downward triangle), lower lip (diamond), or non-responsive (square) sites. The best coefficient of determination is noted above each S1 map. **b** PNI results in a significant loss of cortical somatotopy as measured by best coefficient of determination. ***$p < 0.001$

more slowly along fibers after regeneration, delaying cortical responses (Berry et al. 1944; Cragg and Thomas 1964; Ballantynem and Campbell 1973). Central changes may add to peripheral deficits, as large-scale cortical reorganization involves subcortical sprouting, resulting in increased response latencies within emergent representations (Pearson et al. 2001). While the observed slowing of cortical-evoked responses does not elucidate the origin of these changes in response timing, they serve as a summation of deficits throughout the afferent circuit and likely contribute to sensory dysfunction.

Primary sensory and motor cortices are somatotopically organized, and distorted representations often accompany behavioral deficits following neurological injury (Coq and Xerri 1999b; Xerri and Zennou-Azogui 2003; Ghosh et al. 2009; Martinez et al. 2009). We report a dramatic loss of somatotopy in the digit region of cortex after PNI. Additionally, over half of the digit region in cortex responds similarly to stimulation of three or more digits after PNI, while the uninjured cortex is primarily devoted to preferential responses to an individual digit. Loss of gross somatotopy and uniquely responding cortical areas may contribute to the increased threshold for response to changes in mechanosensory inputs. These results in the rat correspond to the previous reports of cortical responses following nerve repair in primates, as reinnervation, though extensive, is poorly organized (Wall et al. 1986).

Improving sensory function after nerve repair may require restoration of central organization in addition to effective reinnervation (Lundborg 2003; Navarro et al. 2007; Osborne et al. 2018). Distinct changes in S1 somatotopy occur in response to both denervation as loss of original connections reveal latent connections, and reinnervation as new connections to the central nervous system are incorporated (Wall et al. 1986; McCandlish et al. 1996; Florence 1998). Even crush injuries, which spare the integrity of the original nerve sheath, result in degraded cortical organization months following the injury (Barbay et al. 2002). Rehabilitation throughout reinnervation could dynamically shape emerging cortical receptive fields, as even in the more stable uninjured system, somatosensory representations change in response to controlled behavioral manipulations (Recanzone et al. 1992; Xerri et al. 1996; Coq and Xerri 1998, 1999a). The present study suggests that rats may be a useful model organism to study cortical representations following varied rehabilitative strategies after nerve injury.

While the present study provides a characterization of the reorganization of S1 digit responses after nerve injury, a number of limitations need to be considered. First, this study was not designed to systematically assess the time course of changes following nerve repair, and subjects were assessed at a relatively wide range of times after injury. At the chronic stage used, the majority of neurophysiological measures were not correlated with the time post-injury (Fig. S3), suggesting the observed cortical changes are largely stable. However, future studies that systematically evaluate longitudinal changes would allow identification of progressive changes in cortical somatosensory networks arising from nerve injury. Second, mechanical withdrawal threshold was not directly correlated with any neurophysiological measure after nerve injury. This likely indicates that elevations in withdrawal thresholds are not a product of a single feature of cortical function, but rather emerge from the interaction of central and peripheral dysfunction after nerve injury. Third, the cortical sampling density used in this study, while sufficient to identify the robust cortical changes induced by dual nerve transection and repair, was lower than the previous studies, and thus may have been unable to resolve

finer changes in cortical representations. Smaller electrode spacing may be necessary to discern finer patterns of map reorganization after less severe nerve damage and to assess relationships between idiosyncratic map reorganization and sensory recovery.

Our methods for measuring cortical digit representations and map somatotopy differ from classical methods but expand on techniques for recording tactile-evoked potentials used for decades (Hall and Lindholm 1974; Waterhouse and Woodward 1980; Chapin and Lin 1984). A key feature of the present study is the use of 4 mechanical stimulators positioned at a static location on the tips of digits 2–5 of the forepaw throughout each experiment. Reliable mechanical stimulation can be achieved with electromagnetic devices for behavioral and electrophysiological experiments (Waterhouse et al. 1998; Foffani 2004; Corbo et al. 2018). Cortical mapping studies typically use hand-held probes to deliver tactile stimulation, and receptive fields are determined by aural monitoring of evoked neural activity and recorded as a spatial area across the paw (Chapin and Lin 1984; Waters et al. 1995; Xerri et al. 1996; Barbay et al. 2002). While classical methods allow for greater spatial resolution of cortical representations, our current methods allow for quantitative electrophysiological measures of response specificity to stimulation of each digit. By establishing borders of the digit region with standard receptive field definition techniques, our reported digit region closely resembles the size, localization, and organization of well-established literature. The methods used were effective in identifying PNI-related cortical changes and could be used to assess effects of therapies on sensory responses in S1.

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