Radial nerve injury causes long-lasting forelimb sensory impairment and motor dysfunction in rats

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Abstract:

Introduction: Peripheral nerve injury is a common cause of lifelong disability in the United States. Although the etiology varies, most traumatic nerve injuries occur in the upper limb and include damage to the radial nerve. In conjunction with the well-described effects of peripheral damage, nerve injuries are accompanied by changes in the central nervous system. A comprehensive understanding of the functional consequences of nerve injury is necessary to develop new therapeutic interventions.

Objectives: We sought to characterize changes in sensory and motor function and central neurophysiology after radial nerve injury in rats.

Methods: To evaluate somatosensory function in the forelimb, we assessed mechanical withdrawal threshold, spontaneous forelimb use, and cold sensitivity in rats 10 and 16 weeks after radial nerve injury. To evaluate motor function, we assessed performance on a forelimb supination task for up to 16 weeks after nerve injury. Physiological changes in the motor and somatosensory cortex were assessed using intracortical microstimulation and multunit recordings, respectively.

Results: Our results indicate that radial nerve injury causes long-lasting sensory and motor dysfunction. These behavioral deficits are accompanied by abnormal cortical activity in the somatosensory and motor cortex.

Conclusion: Our results provide a novel characterization of functional deficits that are consistent with the clinical phenotype in patients with radial nerve injury and provide a framework for future studies to evaluate potential interventions.

Keywords: Peripheral nerve injury, Radial, Forelimb, Motor, Sensory

1. Introduction

Traumatic injury to peripheral nerves often results in significant disability. Nerve injuries commonly decrease overall quality of life because of motor and sensory dysfunction, particularly when pertaining to the hand.13,22,30 The radial nerve is one of the most commonly injured of the forelimb nerves and leads to the most debilitating consequences.14,36,41 Many patients exhibit a loss of mobility in the supination and wrist extensor muscles. In addition, patients experience loss of sensation to the posterior arm and the dorsal aspect of the hand, which can be accompanied by pain.18,21

A number of preclinical studies have characterized motor and sensory dysfunction after nerve injury in animal models, and the resulting deficits are largely consistent with clinical features of traumatic nerve injury.42 Although most studies focus on injury of nerves in the hindlimb, some preclinical studies have shifted to evaluating forelimb nerve injuries, which is more reflective of the clinical population of traumatic nerve injuries. Damage to the radial nerve accounts for most traumatic nerve injuries in the forelimb; thus, a comprehensive understanding of the consequences of radial nerve injury is necessary to develop interventions.

Several studies revealed long-lasting changes in the central nervous system in response to nerve injury for both the motor and sensory systems.7,12,23,27,38,40,43,44 However, little is known about the nature of these changes in the context of radial nerve injury. We therefore sought to explore central nervous system changes that may accompany radial nerve injury.

In the current study, we sought to develop a model of peripheral nerve injury (PNI) that is representative of what is commonly seen in patients and assessed sensory and motor function after radial nerve injury in a rat model. We observed that radial nerve injuries produce lasting motor and sensory impairments. This behavioral dysfunction accompanies changes in somatosensory and motor cortices. These results provide a novel...
characterization of functional deficits that are consistent with the clinical phenotype in patients who have radial nerve injury. Furthermore, this work provides a framework for future studies to evaluate potential interventions to restore motor and sensory function after damage to the radial nerve.

2. Methods

2.1. Subjects

Thirty-six adult female Sprague-Dawley rats were used in this study, each weighing approximately 250 g. Twenty-two animals were injured, and 14 were used as uninjured controls. Nine nerve-injured animals were used for mechanical sensory testing, cold, cylinder, and grip strength. Eight nerve-injured animals were used for the supination assessment task. Eight nerve-injured animals and 10 uninjured controls were used for sensory neurophysiology. Five nerve-injured animals and 4 uninjured controls were used for intracortical microstimulation (ICMS). All animals were housed in a 12:12-hour reversed light–dark cycle and were food deprived during motor training. All protocols were approved by The University of Texas at Dallas Institutional Animal Care and Use Committee.

2.2. Peripheral nerve injury

Peripheral nerve injuries were performed on the right forelimb. Complete transection of the radial nerve proximal to the elbow followed by tubular repair was performed (Fig. 1). Animals were deeply anesthetized with ketamine hydrochloride (80 mg/kg, intraperitoneally [i.p.]) and xylazine (10 mg/kg, i.p.) and given supplemental doses as needed to maintain areflexia. A small incision on the forelimb proximal from the elbow was made, and the radial nerve was carefully isolated, exposed, and completely transected with microscissors. Immediately after transection, the proximal and distal stumps of the nerve were sutured 1 mm inside the opposite ends of a 6-mm saline-filled polyurethane tube (Micro-Renathane 0.095" I.D. 0.066" O.D., Braintree Scientific, Inc, Braintree, MA), resulting in a 4-mm gap between nerve stumps. The skin incision was sutured and treated with antibiotic ointment. All animals were given a single injection of sustained-release buprenorphine (1.2 mg/kg, i.p.) and enrofloxacin (7.5 mg/kg, i.p.) immediately after surgery.

2.3. Forelimb mechanical sensory test

Mechanical withdraw thresholds were assessed before PNI, 10 weeks after PNI, and 16 weeks after. Testing was performed in an acrylic chamber on a wire mesh floor. Cold withdrawal latency was tested on the right and left forepaws. An ice probe was made by freezing water in a 0.6-ml tube with a plastic applicator stick frozen into the ice for a handle. The ice probe was applied to the plantar surface of the forepaw under the mesh floor, and a stopwatch was used to measure the latency to withdraw from the ice probe. The left paw and right paw were alternately tested, with a minimum 1-minute interval between consecutive tests. The average latency over 5 trials was calculated for each paw.

2.4. Cold withdraw latency test

Withdrawal latencies of the forelimb in response to a cold stimulus were assessed before PNI, 10 weeks after PNI, and 16 weeks after. Testing was performed in an acrylic chamber on a wire mesh floor. A cold probe was made by freezing water in a 0.6-ml tube with a plastic applicator stick frozen into the ice for a handle. The cold probe was applied to the plantar surface of the forepaw under the mesh floor, and a stopwatch was used to measure the latency to withdraw from the cold probe. The left paw and right paw were alternately tested, with a minimum 1-minute interval between consecutive tests. The average latency over 5 trials was calculated for each paw.

2.5. Cylinder forelimb asymmetry test

Spontaneous use of forelimbs during exploratory activity was measured before and after PNI using the cylinder forelimb asymmetry task, similar to previous descriptions. Animals were placed in a clear cylinder (20-cm diameter) and allowed to explore for 3 minutes. Video was recorded from under the cylinder through a clear sheet of acrylic. The total number of both left and right forepaw touches was recorded. An asymmetry index, describing the relative use of the injured forelimb, was calculated as 100 × right forepaw touches ÷ (right forepaw touches + left forepaw touches).

2.6. Grip strength testing

A custom-made grip strength meter was used to measure the grip strength of the right and left forepaws independently, similar to previous descriptions. The rat was positioned over the horizontal bars attached to separate force transducers such that each forepaw grasped a single bar. Rats were held horizontally suspended by their hindquarters and slowly pulled away from the bars until their grip broke. The peak force at which grip was released from the bar was recorded for each paw individually. Five

Figure 1. Images of the radial nerve injury procedure. (A) Illustration of the radial nerve injury in the right forelimb of the rat. (B) A small incision on the forelimb proximal from the elbow was made. (C) The radial nerve was carefully isolated, exposed, and completely transected. (D) The proximal and distal stumps of the nerve were sutured 1 mm inside the opposite ends of a 6-mm saline-filled polyurethane tube, resulting in a 4-mm gap between nerve stumps.
trials were performed at each assessment, and the average of the peak grip forces was recorded.

2.7. Supination assessment task
Animals underwent training in the supination task as previously described.25,28,33 Training sessions occurred twice a day for 30 minutes each, 5 days a week. The behavioral training apparatus consisted of an acrylic cage with a slot in the front right in which animals will reach out of a slot, grasp, and supinate their forelimb to rotate a spherical manipulandum. The manipulandum was affixed to a rotary encoder that provides turn angle measurements. Success rate was defined as trials in which the turn angle exceeds 60°. Training continued until animals achieved a 75% success rate, averaged across 6 consecutive training sessions. Once this criterion was met, animals underwent surgery in which the radial nerve was injured. After a 10-week recovery period, animals were reassessed on the supination task for 10 sessions with at least 50 trials each session, with this data being used for the post-time point in all analyses. Animals continued training for 6 more weeks (16 weeks after injury).

2.8. Primary somatosensory cortex recording and mechanical digit stimulation
Rats underwent primary somatosensory cortex (S1) recordings to evaluate somatosensory responses and cortex organization. Rats were anesthetized with ketamine hydrochloride (75 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.) and mounted into a stereotaxic frame.5 Supplemental doses were administered as necessary. A small incision of the cistern magna was made to attenuate cortical swelling. 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 to 5. The recording procedure was performed as previously described.15 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 to 5 was delivered 20 times at 2 Hz in a randomly interleaved order using the electromagnetic devices described previously.15 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.

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 peri-stimulus time histogram. Driven spikes for each stimulation type were defined as the driven spike rate (mean response period–mean spontaneous period [1–90 ms]) X response duration (end of response latency – onset latency).

2.9. Intracortical microstimulation
Rats underwent ICMS to evaluate left motor cortex organization contralateral to the injured paw, using standard procedures.11,27,34 Rats were anesthetized with ketamine hydrochloride (75 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.), with supplementary doses given as needed to maintain anesthesia levels. Doxapram (20 mg/kg, i.p.) and glycopyrrolate (0.5 mg/kg, i.p.) were given to stabilize breathing and heart rate as needed. A small incision of the cistern magna was made to attenuate cortical swelling. A craniotomy and durotomy was performed to expose the left motor cortex. A tungsten electrode (0.1–1 MΩ) was inserted into the brain at a depth of 1.75 mm. Stimulation sites were then chosen at random on a grid with sites set 500 μm apart from each other.

Intracortical microstimulation procedures were conducted with 2 experimenters to ensure blinding to group and electrode location. The first experimenter placed the electrode and recorded data from each site. The second experimenter, blinded to electrode position, delivered stimulations and classified movements. Each stimulation consisted of a 40-ms pulse train of 10 pulses. Stimulation intensity was gradually increased from 20 μA to 250 μA or until a movement was observed. The stimulation intensity at which a movement was first seen was documented as the threshold. If no movement was seen at 250 μA, then that site was recorded as no response. Movements were classified as proximal forelimb, distal forelimb, or nonforelimb. Cortical area was calculated by multiplying the number of sites eliciting a response by the area surrounding a site (0.25 mm²).

2.10. Statistical analysis
Statistical analysis was performed with MATLAB software. One-way repeated-measures analyses of variance (ANOVA) were used to analyze mechanical withdrawal thresholds, cold sensitivity, grip strength, and forelimb motor performance over time. Post hoc paired t tests were used to determine differences before and after nerve injury. Comparisons were Bonferroni corrected for the number of time points where appropriate. To assess ICMS data and S1 recording data, an unpaired t test was used to determine significance between groups. All data are reported as mean ± SEM. An additional 10 animals failed to demonstrate a forelimb motor deficit, defined previously as an average postlesion baseline performance with at least 30% of trials exceeding 60° on the supination task, and were excluded.33

3. Results
We first sought to evaluate the impact of radial nerve injury on somatosensory function in the forelimb. To do so, we assessed mechanical withdraw threshold, spontaneous forelimb use, and cold sensitivity in rats 10 weeks after transection and gap repair of the radial nerve proximal to the elbow. Radial nerve injury caused long-lasting mechanical hypersensitivity to the ventral surface of the forepaw for up to 16 weeks, as evidenced by a reduction in forelimb mechanical withdrawal thresholds (Fig. 2A, one-way repeated-measures ANOVA, F[2,16] = 12.65, P = 0.0005, post hoc paired t tests, pre vs weeks 10 and 16, P < 0.025). Similarly, radial nerve injury resulted in more rapid withdrawal to a cold stimulus, indicative of an increased sensitivity to cold (Fig. 2B, one-way repeated-measures ANOVA, F[2,14] = 11.66, P = 0.001, post hoc paired t tests, pre vs weeks 10 and 16, P < 0.025). Sensorimotor function was also impaired by radial nerve injury. After injury, rats exhibited an increased reliance on the uninjured forelimb during the cylinder test (Fig. 2C, one-way repeated-measures ANOVA, F[2,14] = 14.087, P = 0.0004, post hoc paired t tests, pre vs weeks 10 and 16, P < 0.025). These results are consistent with other models of PNI.5,43

A number of pioneering studies reveal lasting changes in the central nervous system in response to nerve injury.12,23,40,43,44 but relatively little is known about the nature of these changes in the context of radial nerve injury. Given that radial nerve injury produced chronic deficits in somatosensory behaviors, we sought to examine the effects on somatosensory networks. To do so, we performed multiunit recordings in the primary somatosensory
Radial nerve injury impairs sensorimotor forelimb function. (A) Mechanical withdraw threshold was significantly reduced after radial nerve injury, indicating hypersensitivity to mechanical stimulation. (B) Time to withdraw from a cold stimulus was also reduced after radial nerve injury, indicating sensitivity to cold. (C) Radial nerve injury caused an increased reliance on the uninjured paw in the cylinder task. All plots show group averages (N = 9). Error bars indicate SEM. *P < 0.02.

Fig. 2.

Radial nerve injury caused an increased reliance on the uninjured paw in the cylinder task. All plots show group averages (N = 9). Error bars indicate SEM. *P < 0.02.

Fig. 3.

Radial nerve injury caused an increased reliance on the uninjured paw in the cylinder task. All plots show group averages (N = 9). Error bars indicate SEM. *P < 0.02.
In this study, we sought to develop a rat model of nerve injury that is representative of what is commonly seen in patients with PNI. We report long-lasting forelimb sensory and motor dysfunction after radial nerve injury, which was accompanied by changes to the central nervous system. Together, these findings illustrate that this injury model mirrors common deficits seen in patients with radial nerve injury and provides a framework for development of therapies to target this dysfunction.

Pain is a common complaint that accompanies peripheral nerve damage.\textsuperscript{17,18,29} We find that rats exhibit mechanical hypersensitivity for up to 16 weeks after radial nerve injury. These findings mirror those observed in other nerve injury models in the hindlimb, including the spared nerve injury (SNI) model.\textsuperscript{42,45} In SNI, the common peroneal and tibial nerves of the sciatic branch are injured, causing sensory hypersensitivity for up to 31 weeks in the portion of the hindlimb that is innervated by the intact sural nerve.\textsuperscript{2,45} We sought to extend the SNI model to the forelimb to mimic pain and motor dysfunction that is commonly observed in patients with upper limb nerve injury, specifically radial nerve injury. The current study injured the radial nerve of the forelimb, leaving the median and ulnar nerves intact. Similar to the SNI model, injury to the radial nerve produced long-lasting mechanical hypersensitivity in the ventral side of the forepaw, which is innervated by the intact median and ulnar nerve. We expect that radial nerve injury would produce loss of sensation in the dorsal aspect of the forepaw, which is innervated by the injured radial nerve, but there are no common and well-validated means to test this. Thus, in keeping with our goal of developing a model of forelimb pain, we elected to test the palmar aspect of the paw to test the hyperalgesia of the uninjured median and ulnar nerve. In addition to abnormal mechanical sensation, sensitivity to cold is commonly exhibited by patients with neuropathic pain after nerve damage.\textsuperscript{4,16,24,31} The current study found that radial nerve injury caused long-lasting cold sensitivity, consistent with
These results are consistent with the chronic motor dysfunction observed in patients provides validity for testing interventions to reduce pain after nerve damage in this model.

Sensory dysfunction after nerve damage is often accompanied with long-lasting changes to the central nervous system.3,12,15,23,40,43,44. We explored potential central nervous system changes in the primary somatosensory cortex after radial nerve injury. The current study also found increased spontaneous neural activity and lengthened response durations. Although previous studies observed cortical reorganization after injury to one of the forelimb nerves,15,23,40,43,44 we observed no significant changes in digit organization after radial nerve injury. This likely arises from the fact that the median and ulnar nerves that provide the primary innervation of these networks are still intact. Therefore, the spared input to these circuits may prevent large scale reorganization or changes in evoked strength. In addition, limitations of the recording technique used to evaluate sensory function provide only a relatively coarse and noncomprehensive assessment of evoked sensory activities.

Chronic loss of motor control and diminishment of strength is common after nerve injury.8,21,39–37. The radial nerve provides innervation of muscles involved in rotation of the forearm; thus, patients are often unable to effectively supinate the hand after injury.18. We sought to explore whether similar impairment of forelimb rotation could be measured in rats. Animals with radial nerve injury exhibited lasting reductions in forelimb supination that lasted for at least 16 weeks. In addition to control of forelimb rotation, muscles innervated by the radial nerve are responsible for elbow and digit extension. Consistent with this, previous studies report impairments in reach and grasp tasks in rats after various forelimb nerve injuries.32. Similarly, injury to the median and ulnar nerves which are primarily responsible for grasping caused reduced motor performance for up to 12 weeks on a task that requires an animal to reach out, grasp, and pull on a handle.26. These results are consistent with the chronic motor dysfunction seen in patients.

Previous studies indicate that nerve damage also causes robust motor network reorganization of the forelimb area.2,28,38. We explored whether similar reorganization would co-occur with radial nerve injury. In alignment with previous studies, we observed a reduction in cortical area that evoked movements of the distal forelimb and an expansion in cortical area that evoked movements of the proximal forelimb. Elbow flexion, a proximal movement, is mainly controlled by the intact musculocutaneous nerve, whereas the injured radial nerve controls distal movements involved in supination or digit extension. The expansion of movements controlled by intact nerves at the expense of movements on controlled by the damaged nerve, even after reinnervation, is a common finding.19. Recent evidence highlights the importance of this cortical reorganization in the restoration of motor function after nerve injury.27.

In the current study, we observed that radial nerve injury produced robust motor impairments on a forelimb supination task in 8 animals. However, 10 animals failed to demonstrate a forelimb motor deficit after nerve injury. Compensatory action of other muscles may underlie the absence of an impairment in the observed supination task performance. Because radial nerve injury results in an expansion of proximal movements, it is plausible that compensation with the muscles involved in movements may underlie the absence of behavioral deficits. This expansion may be driven by the intact musculocutaneous nerve, reinnervated fibers from the radial nerve, or a combination thereof. More detailed electromyography recordings in future studies may provide a means to delineate muscle function after radial nerve injury and could be valuable in terms of clinical assessment.

A number of limitations of this study merit consideration. The current study characterized motor and sensory function in a novel rat model of radial nerve injury (PNI) that is representative of what is commonly seen in patients. However, a recent study observed sexual dimorphism in the development of mechanical and cold allodynia after nerve injury.1 Future studies that expand evaluation of radial nerve injury in both sexes will provide a more comprehensive assessment of forelimb dysfunction depicted in this model. In addition, the current study did not include a sham injury group to assess stable performance in the behavioral measures in uninjured animals.

A comprehensive understanding of the functional consequences of nerve injury is necessary to develop new therapeutic interventions. In the current study, we sought to develop a rat forelimb model of radial nerve injury (PNI) that is representative of some aspects of clinical presentation, including loss of motor function and pain. We observed that radial nerve injuries produce lasting motor and sensory impairments. This behavioral dysfunction accompanies changes in somatosensory and motor networks in the brain. Our findings provide a framework for future studies to determine potential interventions that improve impairments after nerve damage, which could improve the quality of life of patients.

Disclosures
The authors have no conflict of interest to declare.

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