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Central Adaptation following Brachial Plexus Injury

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Key words

- Apraxia
- Brachial plexus injury
- Central adaptation
- Nerve trauma
- Neuroplasticity

Abbreviations and Acronyms

BPT: Brachial plexus trauma
CIMT: Constraint-induced movement therapy
CNS: Central nervous system
EMG: Electromyography
ES: Electrical stimulation
H-reflex: Hoffman reflex
MRI: Magnetic resonance imaging
OBPP: Obstetric brachial plexus palsy
PNI: Peripheral nerve injury

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INTRODUCTION

Brachial plexus trauma (BPT) occurs in two different age groups. Obstetric brachial plexus palsy (OBPP) is a recognized complication of childbirth, with an incidence of 0.3% of deliveries.¹ The next peak in the incidence of BPT is in younger (usually male) adults, and it is often caused by motor vehicle accidents or penetrating wounds.²

BPT can result in severe and lasting neurologic impairments, and because the affected patients are young, it has a long-term effect on work and societal roles. As such, optimizing recovery from brachial plexus injury is critical.

Brachial plexus trauma (BPT) often affects young patients and may result in lasting functional deficits. Standard care following BPT involves monitoring for clinical and electrophysiological evidence of muscle reinnervation, with surgical treatment decisions based on the presence or absence of spontaneous recovery. Data are emerging to suggest that central and peripheral adaptation may play a role in recovery following BPT. The present review highlights adaptive and maladaptive mechanisms of central and peripheral nervous system changes following BPT that may contribute to functional outcomes. Rehabilitation and other treatment strategies that harness or modulate these intrinsic adaptive mechanisms may improve functional outcomes following BPT.

RECOVERY FROM BPT

Recovery of nerve tracts following BPT relies on a complex cascade of peripheral nerve regenerative processes, culminating in target muscle reinnervation.³ In instances of severe injury to the brachial plexus or nerve roots, successful nerve regeneration might not be possible without surgical brachial plexus reconstruction.^{4,5}

Even patients in whom regenerating nerve fibers reach the target muscles, there are substantial barriers to a good functional outcome. The process of axonal regeneration is inefficient, and sprouting fibers may not reconnect with the appropriate fascicle beyond the injured segment.^{6,7} Fibers that reach the target muscle do so in substantially reduced numbers, resulting in incomplete reinnervation and a reduced number of functional motor units.⁸ Although the dynamics of motor unit recruitment can recover from nerve injury if the muscle is reinnervated by the same motor nerve,⁹ aberrant reinnervation can affect this process.¹⁰

Maladaptive Central Processes following BPT

Beyond peripheral nerve regeneration, central processes are involved in determining successful or failed functional recovery following BPT.

Developmental Apraxia. The majority of patients with OBPP make an excellent

functional recovery, with no residual deficits identified on serial clinician or physiotherapist review.¹ However up to 15% of patients have persisting significant deficits,¹ and the proportion of patients with spontaneous functional recovery may be overestimated.¹¹

In patients with residual deficits, a pattern of recovery may be seen, with most deficits seen in C5- to C7-innervated muscles. Forearm pronation typically improves before forearm supination.¹² The degree of recovery of shoulder external rotation, elbow flexion, and forearm supination at 3 months predicts which children will retain persistent functional deficits.¹² In children with residual impairment, functional tasks can typically be performed using the injured limb, but with asymmetric movement relative to the uninvolved limb. Elbow flexion and shoulder abduction are the functional movements that prove most challenging in patients after severe OBPP, but shoulder external rotation and forearm supination are usually the most affected movements and recover last.^{12,13} These described patterns of recovery and residual functional impairment inform rehabilitation strategies, although therapy paradigms are largely empiric and are based on splinting of flail wrists and elbows to prevent dislocation and passive range-of-motion exercises to prevent contractures.

In a small subgroup of patients with residual symptoms, electromyography

(EMG) studies of the affected limb demonstrate active motor units in weak muscles, suggesting at least partial reinnervation, but clinical function remains poor.¹⁴ This unique issue has been termed *developmental apraxia* and is considered to be an example of maladaptive central motor programming early in infancy following OBPP.¹⁵ The presence of EMG activity in these clinically weak muscles has been apportioned to “luxury innervation,” which refers to the phenomenon of additional muscle innervation from spinal segments beyond those typical for the individual muscle. As such, a typically C5- and C6-innervated muscle, such as biceps, may have luxury innervation from C7, resulting in the presence of active motor units on EMG with minimal functional movement. Luxury innervation begins between weeks 16 and 25 of gestation and is usually lost after the age of 3 months.^{16,17} Limb immobilization in the period of sensory and motor brain organization, such as following OBPP, can result in incomplete realization of this reserve function, and harnessing this reserve capacity may benefit recovery.¹⁸

Investigations of patients with developmental apraxia identified that reduction of motor skills and muscle strength were exaggerated when compared with neurophysiological and physical muscle responses to peripheral nerve stimulation.¹⁵ This finding was interpreted as being indicative of impaired voluntary motor unit activation, suggesting defective motor programming development in early infancy.

A separate study used transcranial magnetic stimulation to examine a cohort of patients with OBPP without evidence of functional recovery.¹⁸ Motor evoked potentials were recordable in all patients, confirming the presence of an intact connection between the motor cortex and muscle, and suggesting that the failure of functional recovery could be due to abnormalities of central motor control processes.

Illustrative Case 1: Developmental Apraxia

A 17-month-old baby boy suffered a severe left brachial plexus injury at birth resulting in a complete upper trunk palsy on clinical examination. Magnetic resonance imaging (MRI) showed no evidence of nerve root

avulsion. EMG showed no voluntary units in his left biceps and shoulder abductor muscles, but little active muscle denervation. A postganglionic injury of the left upper trunk was diagnosed.

He was taken to surgery and after being anesthetized, electrodiagnostic testing was performed. Transcutaneous stimulation of his left Erb’s region gave rise to contraction of his left biceps, supraspinatus, infraspinatus, and deltoid muscles. Transcranial electrical stimulation (ES) of the right motor cortex also gave rise to motor evoked potential responses in these muscles (Figure 1).

He underwent surgical exploration of his infraclavicular brachial plexus. A supraclavicular brachial plexus exploration was not performed. Direct stimulation of the left musculocutaneous nerve gave rise to contraction in the biceps muscle. Similarly, direct stimulation of the axillary nerve gave rise to a contraction in deltoid.

Because of a lack of functional recovery in elbow flexion, a side-to-side median to musculocutaneous nerve repair was performed to provide a supplementary source of axons to biceps with minimal iatrogenic neurological morbidity.¹⁹ Postoperatively he

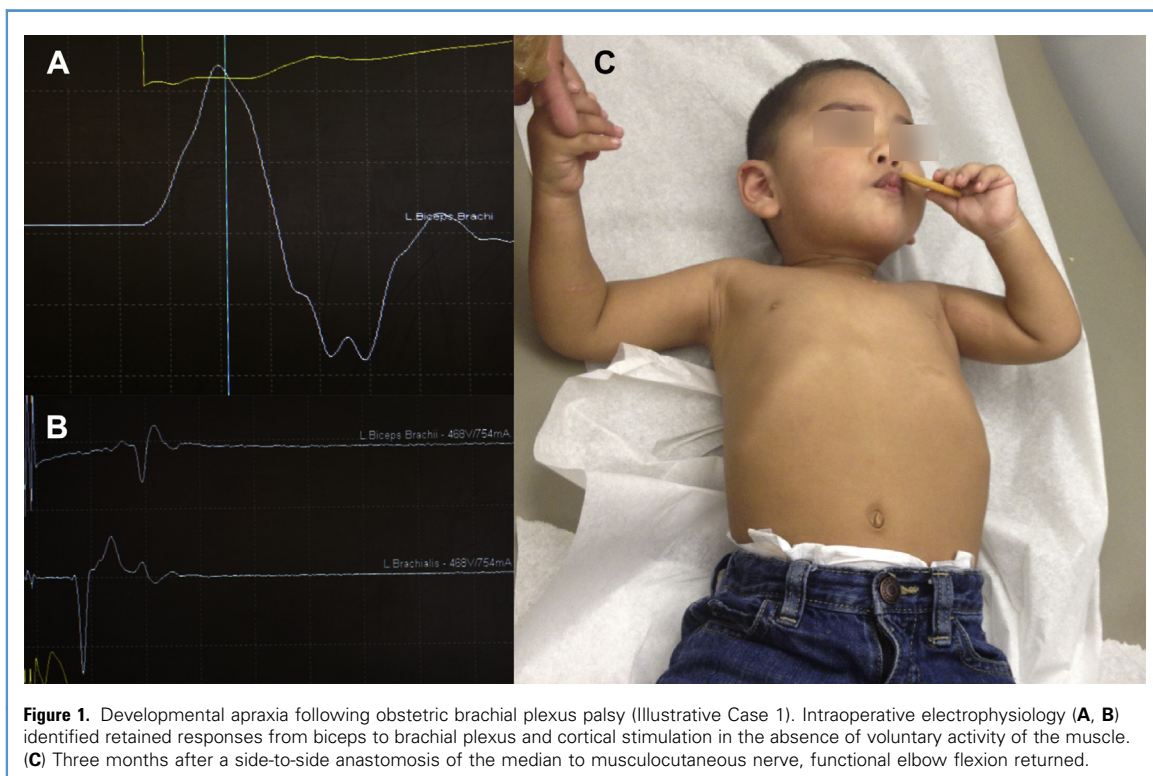


Figure 1. Developmental apraxia following obstetric brachial plexus palsy (Illustrative Case 1). Intraoperative electrophysiology (A, B) identified retained responses from biceps to brachial plexus and cortical stimulation in the absence of voluntary activity of the muscle. (C) Three months after a side-to-side anastomosis of the median to musculocutaneous nerve, functional elbow flexion returned.

underwent weekly transcutaneous ES of the left brachial plexus at Erb's point with contraction of the biceps muscle. At 4 weeks, he showed trace ability to contract his left biceps muscles; by 2 months, he was able to contract his left biceps muscle voluntarily and feed himself. Deltoid function improved spontaneously.

Pain and Neuronal Hyperactivity

BPT in adults is frequently complicated by "nerve pain," which is another example of maladaptive central nervous system (CNS) neuroplasticity. Nerve pain can manifest itself in different ways, including neuropathic and phantom limb patterns.²⁰ Neuropathic pain in the affected limb can range from uncomfortable tingling sensations to intense burning or shooting pains down the arm. On examination, it is characterized by hypersensitivity to painful stimuli (i.e., hyperalgesia) and painful sensations associated with typically nonpainful sensations (i.e., allodynia). Phantom limb pain, which is most often associated with a referred pain perceived in the place of the missing limb of amputees, is also known to occur in deafferented limbs with BPT, typically when adjacent body sites are stimulated. The central mechanisms underlying pain after nerve injuries seem to involve changes in ion channel expression by dorsal root ganglia neurons,²¹⁻²³ intrinsic excitability of dorsal root ganglia neurons,²⁴⁻³⁰ and reorganization at the level of the somatosensory cortex^{31,32} and subcortical structures, such as the thalamus³³ and brainstem.^{34,35} This form of maladaptive CNS neuroplasticity is related to age, because chronic pain rarely occurs in infants with OBPP,³⁶ and it appears to be inversely related to the extent of reinnervation.^{36,37} Reinnervation also corresponds to normalization of deep tendon reflexes after nerve injury, such as can be demonstrated by following the recovery of the Hoffman reflex (H-reflex), the electrical analogue to the monosynaptic stretch reflex.³⁸ The H-reflex is highly facilitated at early stages of reinnervation, but gradually reverts closer to normal levels in the subsequent months after reinnervation.³⁹⁻⁴¹

Brain Remodeling following BPT

Central processes in adults with BPT are less profound than in cases of

developmental apraxia described above, but central adaptation may nonetheless play a role in functional recovery. In general terms, peripheral nerve injury (PNI) initiates rapid changes in cortical activity. In animal models, nerve transection results in rapid silencing of corresponding cortical sensory areas, and equally rapid unmasking of areas corresponding to uninjured hand nerves.⁴² These unmasked areas expand progressively to become detailed representations of the hand, including the adoption of median-innervated skin territories.⁴² There is decreased γ -aminobutyric acid staining in the silenced cortical region, suggesting the mechanism of the evolving cortical plastic changes may be through decreased intracortical inhibition.⁴³ In humans, ischemic median nerve block reduces inhibition at the motor cortical level, producing increased excitability of the corticospinal system.⁴⁴ Of interest, cortical plasticity may be more extensive for gross motor than for fine motor movements, which may contribute to the relatively poor recovery of fine motor control following severe lower brachial plexus injury.⁴⁵

Brain network changes are observed following severe BPT.^{46,47} Following total brachial plexus avulsion causing a functionless limb, resting state functional MRI studies identified cortical reorganization in the hemisphere ipsilateral and contralateral to the side of injury.⁴⁶ Cortical activity changes included motor and premotor areas and brain regions associated with motor task integration (right precuneus) and spatial aspects of motor control (posterior parietal cortex and superior parietal pole).⁴⁶ Of interest, right OBPP resulted in a left-to-right shift of language function.⁴⁷ Brain reorganization was more extensive for dominant than nondominant limb injuries.⁴⁶ Beyond motor cortex changes, further adaptation occurs at spinal and subcortical levels.⁸

Is There a Role for Modulating Central Processes following BPT?

How these experimental findings translate in the clinic is presently unclear. Cortical plasticity can functionally compensate for the lack of specificity in target reinnervation by regenerating axons following severe PNI,⁸ thus optimizing functional

recovery. Disordered motor control may be triggered by abnormal potentiation of sensory inputs and motor outputs.⁴⁸ Exaggerated somatosensory reorganization following nerve injury may be an important mediator of neuropathic pain, such as phantom limb pain following amputation.^{49,50} Finally, recovery from nerve transfer procedures may rely on cortical plasticity. As an example, improved control of biceps was associated with a shift in biceps cortical representation following intercostal to musculocutaneous nerve transfer to treat cervical root avulsion.⁵¹ Controlling the extent of reorganization of sensorimotor circuits may help to focus reorganization toward adaptive processes.⁸

REHABILITATION OF BRACHIAL PLEXUS INJURIES

Current approaches to the rehabilitation of BPT emphasize the mitigation of secondary complications from nerve damage (e.g., contractures, neuropathic pain) and improvement of task performance. These strategies have been reviewed recently,^{52,53} but there remain no proven clinical rehabilitation strategies to enhance nerve reinnervation. There is a growing body of basic science evidence to support specific rehabilitative interventions to accelerate axon regeneration and CNS plasticity.^{54,55}

Sensory Re-Education

The function of the hand depends on the precision of both motor control and sensory feedback. Pioneering work from the groups of Wynn Parry^{56,57} and Dellon⁵⁸ described novel sensory re-education training protocols supported by their observations of good patient outcomes when applied after PNI and repair. This work was inspired by the emerging concepts around neural plasticity during that era⁵⁹ and was widely adopted by the rehabilitation community. In practice, the protocols for sensory re-education can vary. They range from the simple recognition of common objects and textures to pairing tactile stimuli with completely different sensations (e.g., vision) and illusions (i.e., mirror visual feedback) with the hope of achieving activation of the deprived cortical areas.³² Although sensory re-education rehabilitation for BPT has traditionally been

initiated at the first clinical signs of skin reinnervation, more recently it has been explored during the pre-reinnervation phase of recovery.³² Despite the long-standing use of this intervention in rehabilitation of PNI and BPT, it is not clinically established whether improvements with sensory re-education rehabilitation are a result of somatosensory cortex reorganization or simply a practice effect.⁶⁰ Two recent systematic reviews on sensory re-education conclude that it still lacks high-level clinical evidence.^{61,62} Thus, a prospective multicenter, randomized trial of sensory re-education with measurements of hand sensibility, hand function, and patient-reported outcomes would be highly desirable.

Constraint-Induced Movement Therapy

Constraint-induced movement therapy (CIMT) is a well-established approach to managing a paretic limb after stroke⁶³; it has demonstrated at least short-term efficacy in BPT compared with other conventional rehabilitation approaches.⁶⁴ CIMT has undergone many permutations in practice, but it generally consists of three principle components: (1) immobilization of the normal limb; (2) task-oriented training with high repetition; and (3) behavioral strategies aimed at translating skills from the clinical setting to the patient's home environment. Interestingly, much of the original preclinical work underpinning CIMT in for stroke rehabilitation was actually developed in a nerve injury monkey model that caused upper limb deafferentation by dorsal rhizotomy. When a single forelimb was deafferented, the monkey would not make use of the affected limb when it had a choice, despite the intact motor connections⁶⁵; this was termed *learned non-use*. Learned non-use could be overcome with training to use the deafferented limb by restricting movement of the intact limb for several days.⁶⁶ Given the rapid improvements that were observed and the fact that the dorsal rhizotomy paradigm did not permit for peripheral axon regrowth, the mechanism for CIMT has been long attributed to CNS plasticity.⁶⁷ While clinical evidence to support central adaptation as a mechanism for CIMT rehabilitation after stroke has emerged,⁶⁸⁻⁷² it is not clear that this same mechanism is necessarily involved when CIMT is applied to BPT.

There have been no randomized control trials investigating CIMT for BPT, but there are several recent case reports that are suggestive of a potential beneficial effect.⁷³⁻⁷⁶

Exercise

Patients are routinely exercised as tolerated in rehabilitation after nerve injury, but whether this actually improves nerve regeneration is still not known in humans. Perhaps the lack of investigation is a result of early preclinical rodent work showing mixed results from exercise, including no beneficial effect⁷⁷ or even delayed reinnervation.^{78,79} Subsequent work demonstrating increased neurotrophic factor expression after exercise⁸⁰⁻⁸³ appeared to renew interest in the study of exercise on nerve regeneration. More recently, treadmill running in rats with both endurance⁸⁴⁻⁸⁸ and interval^{86,88} training regimens have been shown to promote axon regeneration and to prevent the "synaptic stripping," which is known to occur on motor neuron soma after PNI.⁸⁹⁻⁹² The functional significance of this form of central adaptation from exercise is supported by enhanced recovery of spinal reflexes.^{87,93,94} Although the detail of the optimal exercise prescription has yet to be elucidated, there is some evidence that recommendations may be gender specific^{95,96} and dependent on growth factor upregulation.^{97,98}

Illustrative Case 2: Recovery from BPT

A 34-year-old, right-handed man sustained a severe right brachial plexus injury, leaving him with complete motor deficits in an upper trunk distribution. MRI showed no evidence of nerve root avulsion, and EMG showed extensive denervation in right shoulder abductor and biceps muscles with no voluntary units. At 9 months, he underwent a surgical exploration of his right brachial plexus. The upper trunk was extensively scarred. ES distal and proximal to the scarred portion of upper trunk gave no motor responses. Stimulation of the upper trunk proximal to the scarred portion of upper trunk gave rise to a positive somatosensory evoked potential response over the contralateral cortex demonstrating the presence of axons proximal, but not distal to the scarred segment of upper trunk. The scarred

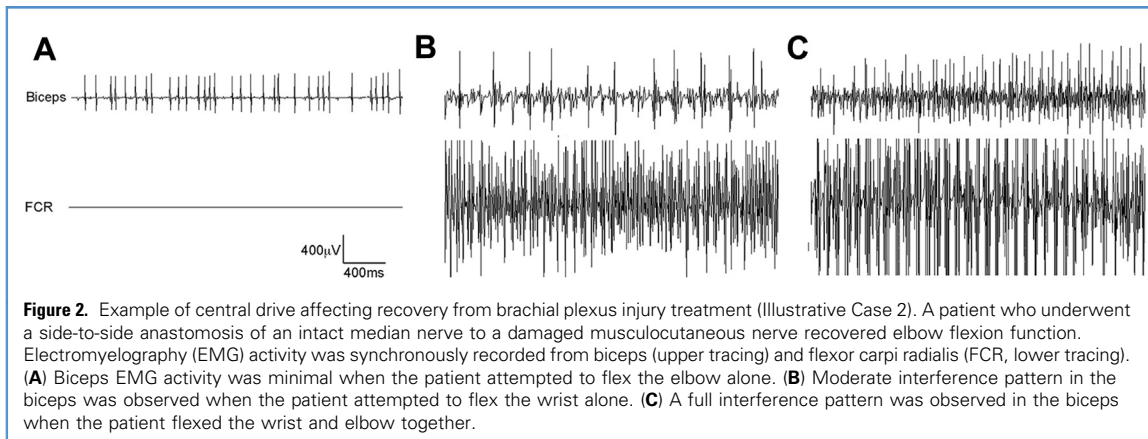
segment was resected, and a 2-cm synthetic bioabsorbable tube was interposed between the proximal and distal ends. Nine months later, nascent voluntary units were seen in the right shoulder abductor muscles (supraspinatus, infraspinatus, and deltoid muscles), but none were found in the right biceps muscle. A second surgery was performed in which the right musculocutaneous nerve was exposed using an infraclavicular approach. Direct stimulation of the right musculocutaneous nerve gave rise to no contraction of the biceps muscles, but did give rise to a somatosensory evoked potential response over the contralateral cortex. The decision was made to perform a side-to-side median to musculocutaneous nerve repair.

After the surgery, the patient underwent physical therapy including constraint-induced movement therapy, limiting the use of the unaffected limb. He received specific motor retraining, focusing on coactivation of biceps and the wrist flexors to facilitate elbow flexion. Nine months later, his right biceps muscle was found to be dually innervated by both his right musculocutaneous and median nerves.¹⁹ Trying to contract his right biceps muscles produced only a grade 1–2 motor response, as did flexing his right wrist. Combining both activities produced a grade 3–4 motor response (Figure 2).

Despite the delay of 18 months from the injury to the second surgery, it was likely that the median nerve axons extended into residual biceps muscle endplates, producing the functional improvements, with successful regeneration of target muscle endplates typically noted within approximately 2 years from a nerve injury.⁴ The rehabilitation strategies described were used with the intention of optimizing functional reorganization after the neurotization procedure,⁵ although it cannot be stated with certainty that they affected functional recovery.

Electrical Stimulation

The emergence of a brief ES protocol delivered as a single-dose treatment (supramaximal stimulation for 1 hour at 20 Hz), developed in the laboratory of Al-Majed et al.^{99,100} and inspired by earlier works,^{101,102} is an excellent example of "bench to bedside" science in rehabilitation



medicine. These findings have been robust and reproduced in several separate laboratories. The results of two small, randomized control trials on patients with severe carpal tunnel syndrome¹⁰³ or traumatic digital nerve transection¹⁰⁴ demonstrated accelerated nerve regeneration and, in the case of the digital nerve injury, improved functional outcomes. Although brief ES has not been applied to patients or preclinical models of BPT, it stands to reason that it might offer similar benefits. Although the primary effect appears to be the augmentation of peripheral reinnervation, there is emerging evidence that brief ES may also improve the recovery of spinal reflexes⁴¹ and work synergistically with treadmill running.⁸⁷ Functional reinnervation after nerve injury requires the re-establishment of appropriately matched axon-target reconnections in the periphery¹⁰⁵ that precedes the re-establishment of central connectivity on motor neurons.¹⁰⁶ Consider that both the precision of reinnervation¹⁰⁷ and the recovery of the monosynaptic stretch reflex circuit¹⁰⁸ recover better after nerve crush than after nerve transection,^{107,109} which underlies how intimately related CNS plasticity is to the restoration of peripheral nervous system connectivity. Finally, although Gordon et al. have successfully developed a single-dose brief ES protocol,¹⁰³ it is not clear whether a single treatment with brief ES would be sufficient to promote nerve regeneration over longer distances required with human brachial plexus lesions. The existing data on brief ES in humans have been accumulated only for distal nerve lesions. The data from preclinical rodent

models deal with regeneration distances of 2–3 cm at the most. Repeated brief ES for brachial plexus lesions provides technical challenges because to date it has been applied to humans with temporary transcutaneous wires applied directly to the epineurium and then removed after the treatment. To this end, Franz et al.¹¹⁰ have developed a brief ES transvertebral stimulation method in mice for transsynaptic activation of lower motor neurons that might better lend itself to reapplication over long durations.

Transcranial Stimulation

Beyond repetitive nerve stimulation, brain stimulation modalities have been explored as a means to improve recovery after PNI, although this approach remains experimental. For example, lasting increases in the excitability of target muscles are produced when transcranial magnetic stimulation of the primary motor cortex is paired with synchronous peripheral nerve stimulation.¹¹¹ Spinal cord stimulation protocols improved peripheral nerve repair and synaptic formation in an animal model of nerve injury.¹¹² Cortical stimulation paradigms have been applied to the treatment of pain after nerve injury in humans, resulting in reduction of chronic pain.¹¹³ However, it is presently unknown whether cortical stimulation results in improved functional recovery after nerve injury, and this approach warrants further investigation.

CONCLUSIONS

BPT can produce severe and lasting deficits through incomplete and inefficient

reinnervation. Evidence is accumulating that central adaptation factors are relevant to the recovery following PNI, and in some instances it can contribute to suboptimal functional outcomes. Modulating CNS responses to peripheral nerve trauma is a component of current rehabilitation strategies. Further research using methods to modulate central adaptation after BPT and other peripheral nerve injuries is suggested to explore this potential therapeutic approach.

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N.G.S. and C.K.F. contributed equally to this work as first authors.

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