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Nerve Injury Triggers Changes in the Brain

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Abstract

It is well known that the adult brain is capable of profound plasticity. Much of our understanding of the mechanisms underlying injury-induced changes in the brain is based on animal models. The development of sophisticated noninvasive neuroimaging techniques over the past decade provides a unique opportunity to examine brain plasticity in humans. In this article, the authors examine the consequences of nerve injury and surgical repair on peripheral nerve degeneration and regeneration and review classic animal literature that laid the foundation of injury-induced plasticity research. They relate these concepts to recent findings of functional and structural changes in the human brain following peripheral nerve injury. They then present a working theoretical model that links behavioral outcomes of nerve injury with functional and structural brain plasticity and personality.

Keywords

plasticity, imaging, nerve injury, thalamus, cortex

Traumatic peripheral nerve injuries (PNIs) can result in sensorimotor dysfunction and/or pain with substantial impairment and disability (Ahmed-Labib and others 2007; Novak and others 2009a, 2009b). Upper extremity nerve injuries are common worldwide and are estimated to comprise 20% of emergency rooms visits (Dias and Garcia-Elias 2006). The economic impact of treating such injuries in the United States is estimated to be $18 billion (Dias and Garcia-Elias 2006). According to the Canadian Institute for Health Information, approximately 2400 PNIs require surgical repair (PNIr, repaired peripheral nerve injury) in Ontario each year, and chronic neuropathic pain is not an uncommon outcome. These injuries significantly reduce quality of life with approximately 25% of patients still out of the workforce 1.5 years after surgery (Jaquet and others 2001; Novak and others 2009b). It is puzzling that some patients have good sensorimotor function following PNIr whereas others do not. The outcome does not seem to reflect the quality of nerve repair or nerve regeneration. However, patient-related factors are considered important contributors to outcome and quality of life after PNI and may include personality and brain structure, connectivity, and function (Novak and others 2009a, 2009b; Taylor and others 2009; Taylor and others 2010).

In this review, we examine the anatomical and functional nerve changes that occur following a PNI and how these changes affect the structure and function of the brain, including the impact on sensory abnormalities and chronic pain.

Peripheral Nerve Injury and Surgical Repair

Nerve Transection, Degeneration, and Regeneration

There are many types of PNI, each resulting in various structural and functional abnormalities. During nerve transection, trophic support from the periphery is arrested, which initiates several changes in the cell body: The volume of the cell body increases, the nucleus is displaced from the center of the cell to a more peripheral location, and Nissl bodies undergo chromatolysis (Fenrich and Gordon 2004; Purves 1986). Chromatolysis involves switching from synthesizing neurotransmitter-related proteins to the synthesis of proteins involved in growth (i.e., neuropeptides, cytoskeletal proteins, and growth-associated proteins). The cell body resembles the embryonic cellular

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environment (Fawcett and Keynes 1990). Peripherally, proximal and distal nerve stumps retract, and cellular contents leak out into the surrounding tissue. In the first week following transection, macrophages are recruited, causing cytolysis and phagocytosis of myelin, which then initiates Schwann cell proliferation (Perry and others 1987). Both Schwann cells and macrophages secrete mitogens and growth factors that are important for successful regeneration and remyelination (Reynolds and Woolf 1993; Terenghi 1999). The proximal stump degenerates back to the first node of Ranvier where new neuronal sprouts are produced within hours (Wong and Mattox 1991). Wallerian (anterograde) degeneration occurs in the distal stump. During this process, the distal axonal segment degenerates, and the myelin sheath that surrounded the axon detaches and degrades, preparing the environment for regenerating axons (Fawcett and Keynes 1990). The degraded products along with macrophage secretions stimulate Schwann cell proliferation within their basal lamina tubes (Salzer, Williams, and others 1980; Salzer, Bunge, and others 1980; Salzer and Bunge 1980). A major function of Schwann cells is the production of neurotrophic factors that are released from the distal stump and diffuse across the injured areas to attract the regenerating axons (Reynolds and Woolf 1993).

During regeneration, the terminal end of the axon swells with smooth endoplasmic reticulum, mitochondria, and microtubules (Fawcett and Keynes 1990). This structure, called the growth cone, was first proposed by Ramon Cajal in the 1890s (Lundborg 2004). Growth cones constantly explore the microenvironment, with extensions known as filopodia and lamellopodia that search for attractant or repulsive molecules (Purves and others 1997). Four basic mechanisms for axonal guidance have been identified: contact-mediated attraction, contact-mediated repulsion, chemo-attraction, and chemo-repulsion (Lundborg 2004; Purves and others 1997). Axons preferentially extend along pathways that they can adhere to, and as a result, growth cones make contact with the old basal lamina and the Schwann cell membranes. Growth cone membranes contain receptors, collectively referred to as integrins, which bind with molecules, such as laminin, fibronectin, cadherins, cell adhesion molecules (CAMs), and trophic factors, located within the extracellular matrix, on other axons, or on nonneuronal cells (i.e., glia). Binding triggers intracellular second-messenger systems and a cascade of events that promote and guide axon extension in a specific direction (Purves and others 1997). In humans, nerve regeneration occurs at approximately 1 to 2 mm/day (Buchthal and Kuhl 1979).

Surgical Repair of Peripheral Nerves

Nerve injuries vary in regard to their severity and outcomes, and several classification schemes have been developed. The Seddon classification describes three types of PNI (Seddon 1943): (1) Neurapraxia refers to a PNI in which there is no conduction across a nerve segment; however, conduction is present in the proximal and distal segments. These nerve lesions are caused by a local loss of myelin (compression or stretching), which interrupts the transmission of action potentials across a specific segment. Remyelination occurs within a few weeks or months, restoring conduction across the injured segment (Kimura 2001; Lundborg 2004). (2) Axonotmesis refers to a loss of continuity within the axon but not the endoneurial tube, usually caused by compression or traction injuries. Following this type of injury, Wallerian degeneration occurs distal to the site of injury. Because the endoneurial tube remains intact, nerve regeneration to its correct distal target follows; the time required for regeneration is dependent on the level of the lesion. (3) Neurotmesis refers to nerve transection in which the epineurium, perineurium, endoneurial tubes, and axons are divided. This injury requires surgical repair. This classification was expanded by Sunderland (1951), who divided neurotmesis into three groups based on the continuity of the connective tissue (i.e., endoneurial, perineurial, and epineurial tissues).

Complete transection interrupts endoneurial tube continuity, and as such, these types of nerve injuries typically have poor functional outcomes. Dykes and Terzis performed a series of nerve crush and transection experiments on baboon ulnar nerves to examine differences between the various types of injuries (Dykes and Terzis 1979; Terzis and Dykes 1980). Following recovery from nerve crush, mechanoreceptor receptive field (RF) shapes and sizes, sensory thresholds, and type of neuronal responses (slowly vs. rapidly adapting fiber types) were almost normal, indicating that regenerating axons reinnervated the same peripheral targets by following their original basal laminae (Dykes and Terzis 1979). Following complete nerve transection (and surgical repair), the recovery time was considerably longer with thresholds remaining elevated 10 months after transection. During recovery from transection, regenerating nerves branch, enter inappropriate distal tubes, and as a result are guided to inappropriate peripheral targets. This results in irregular, small, and dispersed RF representations. By 10 months, these small patchy RFs coalesce into one continuous area. Thus, RF changes could be due to the production of new sprouts and the breakage of old ones until a more normal and unified RF is formed. It was also noted that the near-normal peripheral regeneration following a complete transection did not account for the sensory abnormalities reported years after a PNI in human subjects, raising the possibility that central plasticity may contribute to persistent sensory and motor abnormalities.

Surgical repair of a transected nerve can be performed in several ways, the choice of which is dependent on

the type, size, and location of the lesion. When primary suture repair is not possible, the use of an autologous nerve graft (typically the sural nerve) is the gold standard (Lundborg 2004; Millesi 2007). Although the critical gap length that can be repaired is debatable (Lundborg 2004), it has been suggested that a nerve graft can be up to 6 cm in length without a significant effect on functional recovery (Millesi 2000). The type of nerve graft used has also been related to the functional improvement. Also, the use of motor nerve grafts in the rat, instead of the standard sensory nerve autograft, results in more robust nerve regeneration and a trend toward improved functional outcomes (Moradzadeh and others 2008), possibly related to the larger tubes in motor neurons.

The type of nerve transected may also affect the success of regeneration. In a pure motor or sensory nerve, recovery is generally more successful as axonal misdirection (the growth of a sensory axon into motor Schwann cell basal laminae or vice versa) does not occur (Lundborg 2004). In addition, distal transections facilitate better functional outcomes as regenerating axons do not have to travel as far to reinnervate their peripheral target. The timing of surgical repair is also related to neuronal survival and regeneration (Ma and others 2003). In a study of median nerve transections, results were poor in patients older than age 54 years, with lesions more than 56 cm from the finger tip, delays of more than 24 months from injury to surgery, and graft lengths greater than 7 cm (Kallio and Vastamaki 1993).

There are conflicting findings pertaining to the impact of age on functional recovery. Many studies report that recovery is best in children, with limited recovery in adults (Jerosch-Herold 2003, 2005; Lundborg and Rosen 2001; Rosen and others 2000), perhaps because of the shorter distances that regenerating axons must grow to innervate distal targets in young individuals. However, when nerve transections were surgically repaired in adult or infant monkeys, the total number of myelinated fibers and the conduction velocities of the nerves were not different between the groups when tested several years later (Almquist and others 1983). This suggests that peripheral nerve regeneration is equivalent in the young and old and that functional outcomes may be related to the capacity for central adaptation to new afferent input. Interestingly, Lundborg and Rosen's (2001) results demonstrating decreased tactile gnosis with increasing age correlated with previously published data demonstrating decreased language acquisition abilities in immigrants with increasing age. Finally, recovery of sensory function has been found to be strongly related to verbal learning and visuospatial capacity (Rosen and others 1994). These studies suggest that central processes relating to plasticity and learning may account for some of the variability in functional recovery following nerve transections.

Development of Pain following Nerve Transection

Peripheral nerve transection results in the loss of sensorimotor function in the area of innervation of the transected nerve. These negative symptoms of nerve transection occur immediately following the injury. Transection of a nerve stimulates regeneration of the nerve and occasionally leads to the development of additional (positive) symptoms, such as paraesthesia, spontaneous and/or evoked pain with hyperalgesia, and allodynia (Jensen and Baron 2003). This pain is considered to be neuropathic as it is "pain initiated or caused by a primary lesion or dysfunction or transitory perturbation in the peripheral or central nervous system" (IASP Task Force on Taxonomy 1994). This definition highlights the central and peripheral components of neuropathic pain.

Several potential peripheral mechanisms may lead to the development and maintenance of neuropathic pain. Animal models used to study these mechanisms include (1) chronic constriction injury, whereby four sutures are loosely tied around the sciatic nerve, causing swelling and strangulation of the nerve; (2) spinal nerve ligation, typically tight ligation of spinal nerves at L5 and L6; (3) axotomy, involving a nerve transection (usually the sciatic nerve); (4) partial sciatic nerve ligation, whereby a suture is placed though one-half to one-third of the sciatic nerve; and (5) spared PNI, involving ligation of the common peroneal and tibial nerves while sparing the sural branches of the sciatic nerve (Bennett and Xie 1988; Decosterd and Woolf 2000; Kim and Chung 1992; Ossipov and others 2006; Seltzer and others 1990; Wall and others 1979). These models result in behavioral signs of spontaneous and evoked pain (mechanical and cold allodynia) that can be assessed with standardized sensory testing techniques. In addition, they have provided a wealth of information regarding the underlying cellular and molecular mechanisms leading to the development of neuropathic pain and have helped to explain the actions of analgesic drugs.

These animal models have identified ectoptic pain-related activity generated at several locations in the PNS (Campbell 2001; Devor and Rappaport 1990). One such site is the location of the injury itself. Following nerve transection, there is a short-lived (approximately 2 minutes) barrage of activity in the proximal portion of the transected nerve up to the dorsal horn (Wall and others 1974). A nerve transection interrupts the flow of trophic molecules to the cell body and initiates a cascade of events that essentially changes the cell from a state of maintenance to one of growth and regeneration. Regenerating sprouts emerge for the cut end and begin to elongate. If surgical repair is not performed and contact is not made with the distal basal membrane, these regenerating sprouts form a tangled mass known as a neuroma. Even

with surgical repair or an incomplete transection, a neuroma-in-continuity may develop when some of the regenerating axons become tangled and do not regenerate successfully. Light pressing on this structure will elicit pain and the Tinel sign (i.e., paresthesia and sharp pain in the distribution of the nerve). The neuroma has spontaneous activity with unusual properties (Wall and Gutnick 1974). Devor and Govrin-Lippmann (1983) demonstrated that in neuromata of mixed nerves, the majority of spontaneous activity stemmed from sensory nerves, as opposed to motor or sympathetic nerve types. Furthermore, a higher proportion of Aβ- and Aδ-fibers are spontaneously active compared with C-fibers (Liu and others 2000), although A-fibers may contribute to spontaneous activity at short posttransection time points, with C-fibers dominating at longer posttransection time points (Devor and Rappaport 1990). There may also be differences in the firing patterns of these different fiber classes. Most spontaneously active A-fibers discharge with a rhythmic firing pattern between 15 and 30 Hz that can increase to 200 Hz with mechanical stimulation, whereas spontaneous C-fiber activity is characterized by slow and irregular firing (Devor and Rappaport 1990). The spontaneous activity and rhythmic firing patterns are the result of an abnormal accumulation and insertion of sodium channels, as well as other membrane-bound proteins involved in transduction and propagation, within the neuroma end bulb. This results in abnormal hyperexcitability of the neuroma, leading to intense pain.

Ectopic activity has also been demonstrated in dorsal root ganglia (DRG) in intact and acutely transected axons (approximately 5% of axons tested), and a greater proportion of axons showed ectopic activity 3 months after the initial transection (Wall and Devor 1983). Another study showed that most of the DRG axons with ongoing activity have nerve conduction velocities in the Aδ range following gastrocnemius soleus nerve transection, but not sural nerve transection, suggesting that afferents supplying the skeletal muscle (but not the skin) generate ongoing activity (Michaelis and others 2000). Again, it is likely that sodium channel up-regulation (in particular the TTX-sensitive type III sodium channel; Waxman and others 1994) in the DRG, following axotomy, enhances excitability and leads to ongoing discharges.

The intact nociceptor has also been proposed as a site for ectopic activity. This could occur peripherally in the skin where there is partial denervation (i.e., where there is some overlap from transected and normal nerves) or in the intact fiber (Campbell 2001). During Wallerian degeneration, the neighboring intact nerves could be exposed to molecules involved in degeneration and regeneration of the transected nerves. This exposure leads to changes in the membrane properties of the intact nerve fibers and may initiate spontaneous activity. Thus, ectopic activity and neuropathic pain may originate at several peripheral sites in the intact and/or transected nerve. The contribution of spontaneous activity generated at these different sites adds to the complexity of diagnosing and treating neuropathic pain. In addition, genetic differences may contribute to intersubject variability in the expression and maintenance of neuropathic pain states (Mogil 1999).

Central Plasticity Induced by Nerve Damage

Central plasticity refers to changes that occur in the CNS over time. It was once thought that only the developing nervous system possessed the capacity to undergo plasticity. However, pioneering studies established that rapid plasticity is possible in the adult CNS and that these changes can occur throughout the CNS in the spinal cord, the dorsal column nuclei, the thalamus, and the cortex. It is now widely accepted that the adult nervous system retains some capacity for change. Plasticity can be beneficial or maladaptive. As described above, a damaged nerve can cease to function or convey abnormal ectopic activity to the CNS. The response of the CNS to altered peripheral inputs may take many forms, including changes in ongoing or stimulus-evoked activity, receptive field properties, and gray matter or white matter connectivity, with concomitant effects on perception, behavioral, cognitive, and/or sensorimotor function (see Box 1 and Fig. 1). MRI-based functional and structural techniques can now be used to assess brain plasticity and the impact of individual factors following PNI (see Box 2).

Box 1

Indicators of CNS plasticity following peripheral injury:

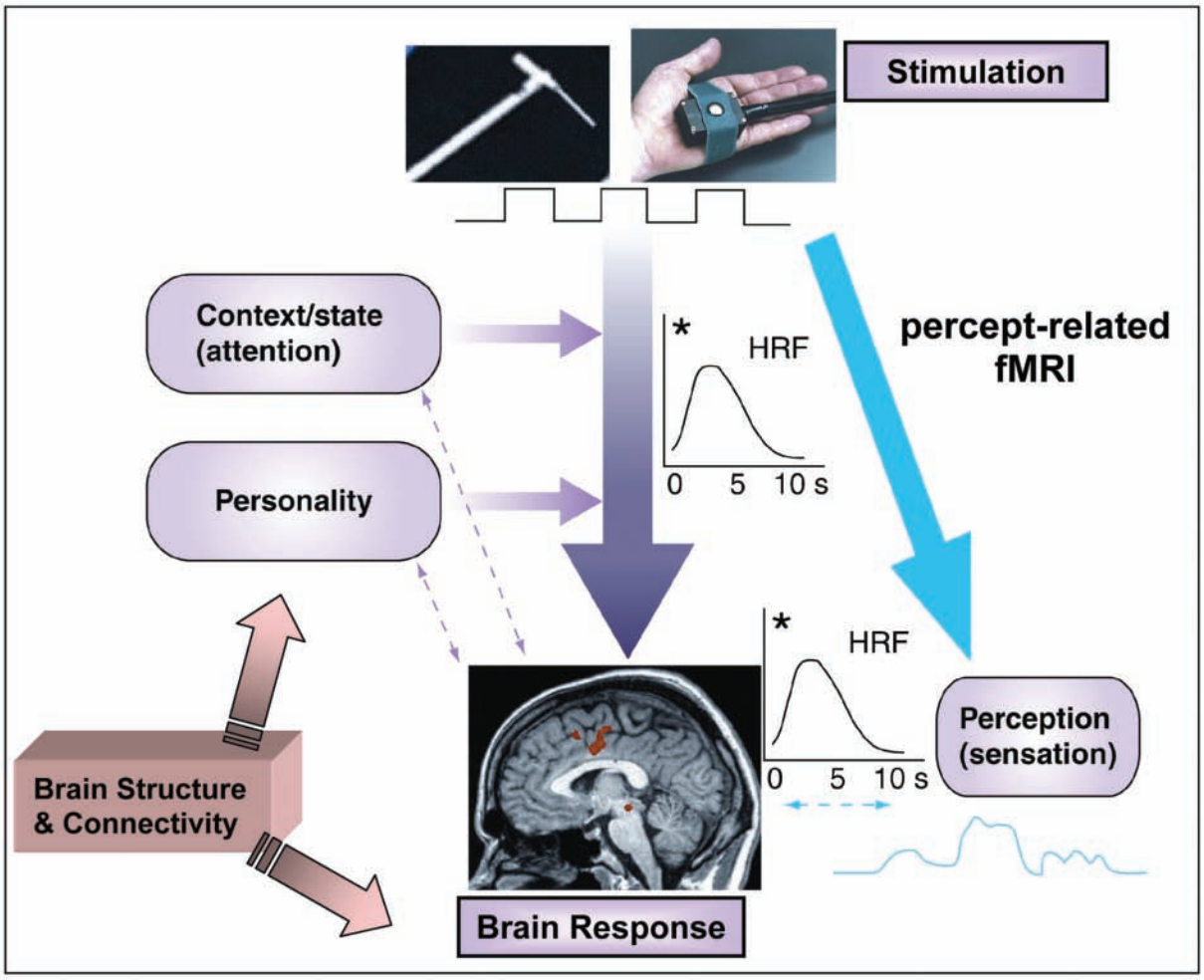
- Spontaneous neuronal activity
- Abnormal neuronal responsiveness (stimulus-evoked activity and sensitivities)
- New neuronal receptive fields
- New stimulus-evoked projected fields (human studies)
- Changes in somatotopy
- Gray matter loss/gain
- White matter loss/gain
- Abnormal functional or structural connectivity between brain regions/networks

Potential neuronal mechanisms of CNS plasticity:

- Unmasking/strengthening of silent or ineffective synapses
- Collateral sprouting
- Loss of GABAergic inhibition (i.e., disinhibition)
- Loss of temporally correlated activity

Box 2

Noninvasive MRI-based approaches to study brain plasticity in humans. Functional MRI is a popular method that can be used to assess brain responses to a sensory stimulus or the perception evoked by that stimulus (percept-related fMRI). Correlations between these responses and factors such as attention, personality, and brain structure (gray matter) and connectivity (white matter) can also provide insight into brain-behavior relationships. HRF = hemodynamic response function. * = mathematical convolution. Adapted with permission from Davis (2006).



Animal Studies of Plasticity

One of the first reports of plasticity in the adult mammalian CNS found that neurons in the ventral posterolateral nucleus (VPL) of the thalamus that had once responded to stimulation of the leg became responsive to stimulation of the arm seven weeks after ablation of the dorsal column nucleus gracilis (Wall and Egger 1971). This remodeling was attributed to collateral sprouting from the terminal arborizations of intact neurons in the cuneate nucleus. Another study then reported that immediately following transection of the dorsal roots caudal to L4, there was an increase in the proportion of nonresponsive gracile nucleus neurons and that the representation of the intact afferents in the gracile nucleus was larger than expected (Millar and others 1976). Eight months later, the proportion of unresponsive cells had decreased, and there was an additional increase in the representation of the intact afferents. Thus, latent connections may exist that immediately become unmasked by partial deafferentation, and the efficacy of these connections may strengthen with time. Another study found comparable receptive field changes of gracile

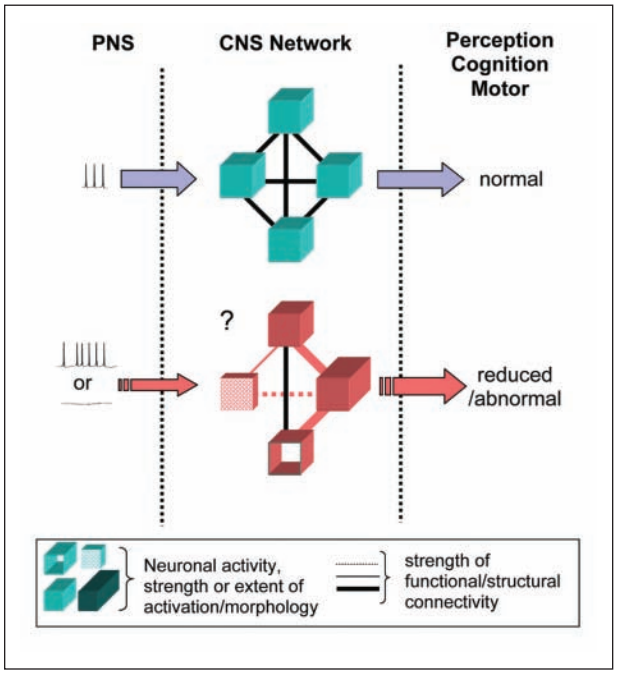


Figure 1. Abnormal peripheral activity induces central plasticity. Peripheral nerve injuries (PNIs) can generate abnormal or ectopic activity that is conveyed into the CNS. The proposed response of the CNS includes changes in (1) ongoing neuronal activity, the pattern and/or sensitivity of evoked neuronal activity; (2) gray matter; (3) functional connectivity between brain areas; or (4) white matter connectivity between brain areas. This central plasticity can affect sensory, motor, and cognitive behaviors.

neurons (i.e., a switch from leg to abdomen receptive fields) induced by a reversible cold block to the dorsal columns in cats and further reported that the receptive fields reverted to their original location when the dorsal column cold block was removed (Dostrovsky and others 1976). These findings highlight the speed with which these central neuronal changes can occur, supporting the theory that plasticity is caused by unmasking of normally silent synapses.

Plasticity in the spinal cord dorsal horn and at supraspinal levels following PNI is also well established. Basbaum and Wall (1976) produced a partial deafferentation by sectioning the dorsal roots caudal to L3 and found that the projection zone of the sectioned afferents was initially unresponsive to tactile stimulation (within the transected peripheral area or adjacent territories). However, this unresponsive region became responsive to stimulation of the adjacent territories within one to four weeks. Dorsal horn neuronal changes also occur when the sciatic and saphenous nerves are sectioned (Devor and Wall 1978, 1981). Plasticity in the primary somatosensory cortex (S1) was also found following dorsal root sectioning; again, the pattern of reorganization reflected the expansion of adjacent body parts into the deafferented cortex (Franck 1980). The aforementioned studies were all performed in the cat, and subsequent studies in primates corroborated the concept that functional plasticity can occur at any level of the neuroaxis.

The normal cortical representation of cutaneous afferent information within Brodmann area (BA) 3b and 1 of S1 is arranged somatotopically with discrete representations for each digit that are organized in a medial to lateral order (i.e., the small finger is located more medially and the thumb located more laterally). In addition, single neurons usually have small receptive fields restricted to single digits. Immediately following median nerve transection and ligation, the deafferented cortical territory is composed of patches of unresponsive cortex mingled with areas that respond to stimulation of adjacent peripheral nerve territories (Merzenich, Kaas, Wall, Sur, and others 1983; Merzenich, Kaas, Wall, Nelson, and others 1983). These responses possess a crude somatotopy that transforms into a highly topographic representation over time. In some of these cases, the entire ulnar nerve representation appeared in the deafferented cortical space; often the deafferented cortex was completely reoccupied within 22 days of nerve transection. A similar pattern of cortical plasticity was observed in adult owl monkeys that underwent amputation of the middle or index finger; again, electrophysiological evidence demonstrated that the adjacent remaining digits and palmar surfaces expanded into the deafferented cortical territory (Merzenich and others 1984). One year following median nerve transections that were permitted to regenerate, the deafferented cortex retained a patchy discontinuous representation of the transected and adjacent nerves (Wall and others 1986). The time course of plasticity following digit amputation in flying foxes (Calford and Tweedale 1988) and peripheral nerve transection in rats (Cusick and others 1990) also revealed the rapid unmasking of previously silent or ineffective synapses.

A GABA mechanism is thought to be responsible for these rapid changes since transection and ligation of the median and ulnar nerves produced a dramatic reduction in S1 GABA staining that spanned all cortical layers but was restricted to the deafferented cortical territory (Garraghty and others 1991). These data suggest that rapid unmasking of previously silent inputs is the result of a loss of GABAergic inhibition originating from the deafferented neurons. This type of plasticity is thought to account for changes that occur over fairly small distances (1-2 mm) where the projection zones of individual thalamocortical axons overlap (Pons and others 1991).

Cortical reorganization can also occur over large distances. For example, transection of both median and ulnar nerves produces large-scale cortical reorganization with

no unresponsive areas, with complete reinnervation by the remaining adjacent nerves (Garraghty and Kaas 1991). Also, there were large-scale cortical reorganizations following deafferentation of an entire limb, with the entire cortical representation of the upper limb (normally occupying 10-14 mm) becoming responsive to stimulation of the face 12 years after deafferentation (Pons and others 1991). As terminal arborizations are not thought to extend over such large areas, it has been proposed that sprouting at cortical or subcortical levels may account for the cortical magnification of plasticity. Another study (Florence and Kaas 1995) examined animals that had undergone therapeutic amputation of the hand or forelimb up to 13 years earlier and found that the stump and proximal forelimb on the amputated side innervated unusually extensive regions of the spinal cord and cuneate nucleus and that the cortical areas that had been responsive to hand or forearm stimulation had become responsive to stimulation of the forelimb and shoulder. These findings were attributed to sprouting within the spinal cord and cuneate nucleus. Subsequent tracing studies in rats and monkeys support the view that sprouting of intact afferents at the level of the dorsal horn, dorsal column nuclei, and cortex may account for large-scale reorganization (Bao and others 2002; Dancause and others 2005; Hickmott and Steen 2005; Jain and others 2000; Sengelaub and others 1997; Wu and Kaas 2002).

The temporal pattern of afferent activity may also shape the CNS and contribute to abnormalities if disrupted. For example, after surgically connecting the skin surfaces of two adjacent digits (syndactyly), the digit representation in S1 was no longer discrete but appeared as a fused zone responding to stimulation of both digits (Allard and others 1991; Clark and others 1988). A series of studies examined the effect of increased afferent input on plasticity within primate S1 (Flor and others 1997; Recanzone, Jenkins, and others 1992; Recanzone, Merzenich, and Jenkins 1992; Recanzone, Merzenich, and Schreiner 1992). The animals were trained to detect frequency differences in serially applied tactile stimuli and over a period of 20 weeks learned to accurately discriminate between frequencies that differed by only 2 to 3 Hz (initially they could only discriminate between frequencies that differed by 6–8 Hz). These behavioral improvements in frequency discrimination were accompanied by cortical changes in BA3b that included increased complexity of the cortical representations, a 1.5- to 3-fold increase in cortical representation of the stimulated skin location, and larger receptive fields within the trained region. Changes were also observed within BA 3a in that the representation of the deep receptors was replaced with a representation of the trained cutaneous region. These findings were thought to reflect strengthening of synapses based on behaviorally relevant and temporally correlated inputs.

In summary, these studies clearly demonstrate that the adult mammalian CNS undergoes plasticity that can be induced by deafferentation or by increased afferent input, which may reflect behaviorally relevant input. Plasticity may be beneficial by allowing an organism to adapt to and learn about its environment, but it can also be maladaptive and lead to behavioral deficits.

Human Studies of Functional Plasticity

Prior to the advent of modern neuroimaging, there were few opportunities to study brain plasticity at the neuronal level in humans directly. However, Davis and others (1998) used intraoperative single-cell recordings and microstimulation to investigate neuronal plasticity at the level of the thalamus in patients who had undergone limb amputation (see Fig. 2). In the normal sensory thalamus, a large region contains neurons with receptive fields in the hand (i.e., neuronal responses are evoked when tactile stimuli are applied to the hand), and a very small region contains neurons with receptive fields in the more proximal upper arm/shoulder. Thalamic microstimulation normally evokes a sensation (i.e., projected field) that appears to arise from the receptive field of the neurons at that site. However, thalamic mapping in patients who experienced phantom sensations identified a large number of neurons that either had no receptive field or responded to touching the upper arm/shoulder, and microstimulation at these sites evoked feelings in the missing (phantom) hand. Interestingly, microstimulation never evoked feelings in the phantom in patients who never experienced phantom sensations. These data indicate that following nerve injury associated with amputation, thalamic neurons lose their normal input (receptive field) and can become responsive to other inputs, either through sprouting or unmasking of previously ineffective inputs. Furthermore, the output of these neurons can signal these new inputs. It is not clear whether such reprogramming is adaptive or maladaptive.

The development of modern neuroimaging has provided new opportunities to examine human brain plasticity. One of the earliest studies of human cortical plasticity was performed with magnetoencephalography in patients undergoing surgery for the separation of webbed fingers (i.e., syndactyly) (Mogilner and others 1993). By modeling the dipole locations in response to tactile stimulation of each digit before and after surgery, cortical reorganization was demonstrated over 3 to 9 mm. Originally, dipole representations overlapped during stimulation of the fused digit; however, within weeks of surgery, discrete dipole representations could be resolved. In another interesting study, serial fMRI in a patient whose left big toe was transferred to the hand following amputation of the right thumb (Manduch and others 2002) revealed that at

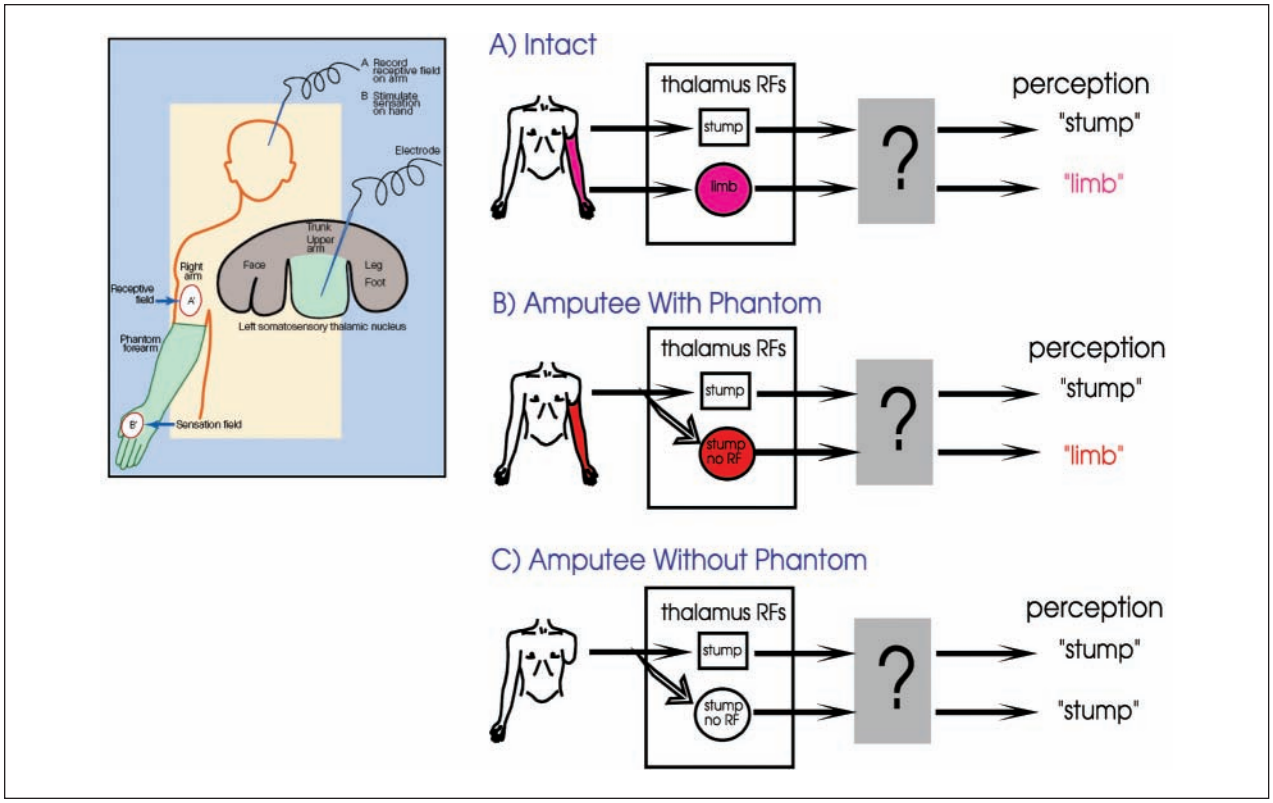


Figure 2. Neuronal plasticity following amputation. Intraoperative electrophysiological recordings and microstimulation were carried out in patients undergoing surgery for postamputation pain. *Left panel:* Experimental paradigm that included microelectrode neuronal recordings in the sensory thalamus to determine neuronal receptive fields and microstimulation through the recording electrode to determine the perceptual effect of stimulating the neurons (with permission from Kaas 1998). *Right panel:* Potential mechanism underlying reprogramming of neuronal function following limb amputation. Model is based on findings of sensory thalamic neurons without receptive fields (RFs) or new proximal receptive fields and thalamic stimulus-evoked sensations in the missing (phantom) limb (in patients with phantom sensations) and in the stump (in patients who did not experience phantoms) (for details, see Davis and others 1998).

functional recovery time points, such as the return of active movement (week 5) and sensation (week 14), motor cortex (M1)/S1 activation increased and gradually normalized to the same level as controls at 115 weeks postsurgery. These findings may represent a "signature" of good functional motor outcomes.

These studies demonstrate that adaptive cortical plasticity can occur following injury and that this plasticity may be associated with behavioral changes. However, not all cases of plasticity following a PNI are adaptive. For example, in one study, patients who developed carpal tunnel syndrome also developed blurring between the cortical representations for the affected digits (Napadow and others 2006). An fMRI study found reorganization in M1 and S1 in amputees who experienced phantom limb pain (PLP; Lotze and others 2001). The data demonstrated that the lip representation moved into deafferented hand areas only in amputees who experienced PLP. These changes were proposed to represent a neural correlate of PLP and thus represent a maladaptive form of cortical plasticity. This group also reported that frequent use of a myoelectric prosthesis negatively correlated with cortical reorganization of the lip into deafferented cortical areas and positively correlated with decreased PLP, suggesting that visual feedback, ongoing stimulation, and muscular training of the stump may prevent maladaptive cortical plasticity in amputees.

Measuring Gray and White Matter Plasticity in Humans

The classic animal literature discussed earlier laid the foundation for investigating structural brain plasticity following PNI. Specifically, animal models of PNI suggest that functional abnormalities may be accompanied by morphological changes in the brain. The standard methods to examine gray or white matter integrity involved time-consuming histological analysis or tract tracing techniques

that were limited to small brain regions, usually during postmortem study. The newer MRI-based approaches now provide the opportunity to examine the structure of the human brain in vivo. These new technologies have revealed gray and white matter changes in the brain associated with a variety of conditions, including PNIs.

The most widely used approach to examine gray matter plasticity from MRI images is voxel-based morphometry (VBM; Ashburner and Friston 2000). VBM tests for statistically significant differences in regional gray matter density (i.e., partial volume effect due to gray matter) between subject groups. VBM has identified gray matter differences attributed to neurological conditions (Betting and others 2006; Wessels and others 2006) and personality factors such as neuroticism and extraversion (Omura and others 2005). Complementary to VBM is cortical thickness analysis (CTA), which provides a quantitative measure of cortical thickness in millimeters. CTA has been used to interrogate cortical thickness in healthy subjects and in patient populations (Fischl and Dale 2000; Jang and others 2006; Luders and others 2006). CTA and VBM are complementary since VBM reports statistical maps of differences in gray matter density (relative to other tissue types) in cortex and subcortical areas, and CTA outputs scalar values (mm of cortex). The meaning of changes in gray matter volume, density, or thickness detected with MRI is not clear but likely related to alterations in neuronal or glia cell size or changes in axonal architecture (such as synaptogenesis) (May 2008). Some support for these suggestions comes from a recent study by Metz and others (2009). Following a spared PNI (a model of neuropathic pain), neurons in the contralateral medial prefrontal cortex of rats possessed altered functional (as measured by increased *N*-methyl-D-aspartate [NMDA] currents) and morphological (measured as an increase in basal dendrites) changes (Metz and others 2009). The findings were attributed to the gray matter reductions typically observed in human morphometry studies by suggesting that increased NMDA currents and increased basal dendritic spines may lead to glutamatergic input-mediated calcium entry, which ultimately may cause excitotoxicity and neuronal loss. Finally, gray matter plasticity in the brain following PNI may be a time-dependent process. For example, deafferentation induced by limb amputation was associated with reduced gray matter density within the contralateral thalamus that was positively correlated with the time span since amputation (Draganski and others 2006).

Brain plasticity may also occur with white matter changes such as demyelination or axonal degeneration (Beaulieu 2002). White matter can be assessed in humans with a special type of MRI acquisition called diffusion tensor imaging (DTI). DTI is a technique in which the MR signal is made sensitive to the diffusion of water molecules. Diffusion of water molecules that is equal in all directions is known as isotropic diffusion, whereas the diffusion of water molecules preferentially in one direction is called anisotropic diffusion. In the brain, water molecules confined within or between white matter tracts tend to diffuse parallel to the fiber (axon) tracks. This is caused by cellular barriers imposed by myelin and intracellular structures, such as neurofilaments, that tend to impede perpendicular diffusion (i.e., perpendicular to the long axis of the axons). Gray matter and ventricles have less structural organization, and as a result, water diffusion is more isotropic in these brain areas. By manipulating MRI acquisition parameters, diffusion of water can be used to delineate connectivity and integrity of white matter structures (Mori and Zhang 2006). Most commonly, fractional anisotropy (FA) is computed and assessed, although other measures such as mean diffusivity (MD) and relative anisotropy (RA) can provide important information. DTI is now widely used to examine white matter pathways in the normal in vivo human brain and white matter changes following injury and recovery. Many factors contribute to DTI measures. Theoretically, any longitudinally orientated barrier could contribute to anisotropy, such as cell membranes, intracellular microtubules, neurofilaments, and myelin (Beaulieu 2002). However, Beaulieu (2002) proposed that the major source of anisotropy in neural tissue is the axonal cell membranes themselves. Importantly, several studies support the idea that FA, RA, and MD provide information about axonal integrity and myelination and that parameters that specifically investigate parallel or perpendicular diffusion may be specific markers for axonal degeneration (or axonal integrity) and myelination, respectively (Budde and others 2007; Kim JH and others 2007; Song and others 2002; Song and others 2003; Song and others 2005).

Linking Behavior with Functional and Structural Plasticity following PNI

Our group has examined the impact of PNI on brain function and structure (Taylor and others 2009, 2010; see Figs. 3–5). We tested a group of patients at least one year after they had sustained a complete transaction of the median or ulnar nerve and undergone microsurgical repair of the nerve. The sensory and motor nerve conduction testing showed increased latency and/or decreased amplitudes, indicating that the patients did not regain normal peripheral nerve function. These lingering peripheral nerve abnormalities were associated with profound behavioral abnormalities, including sensory deficits (tactile, vibration, and shape detection) and reduced dexterity and sensorimotor integration skills. The patients also showed abnormal functional MRI digit vibration-evoked responses within cortical areas related to somatosensation and attention.

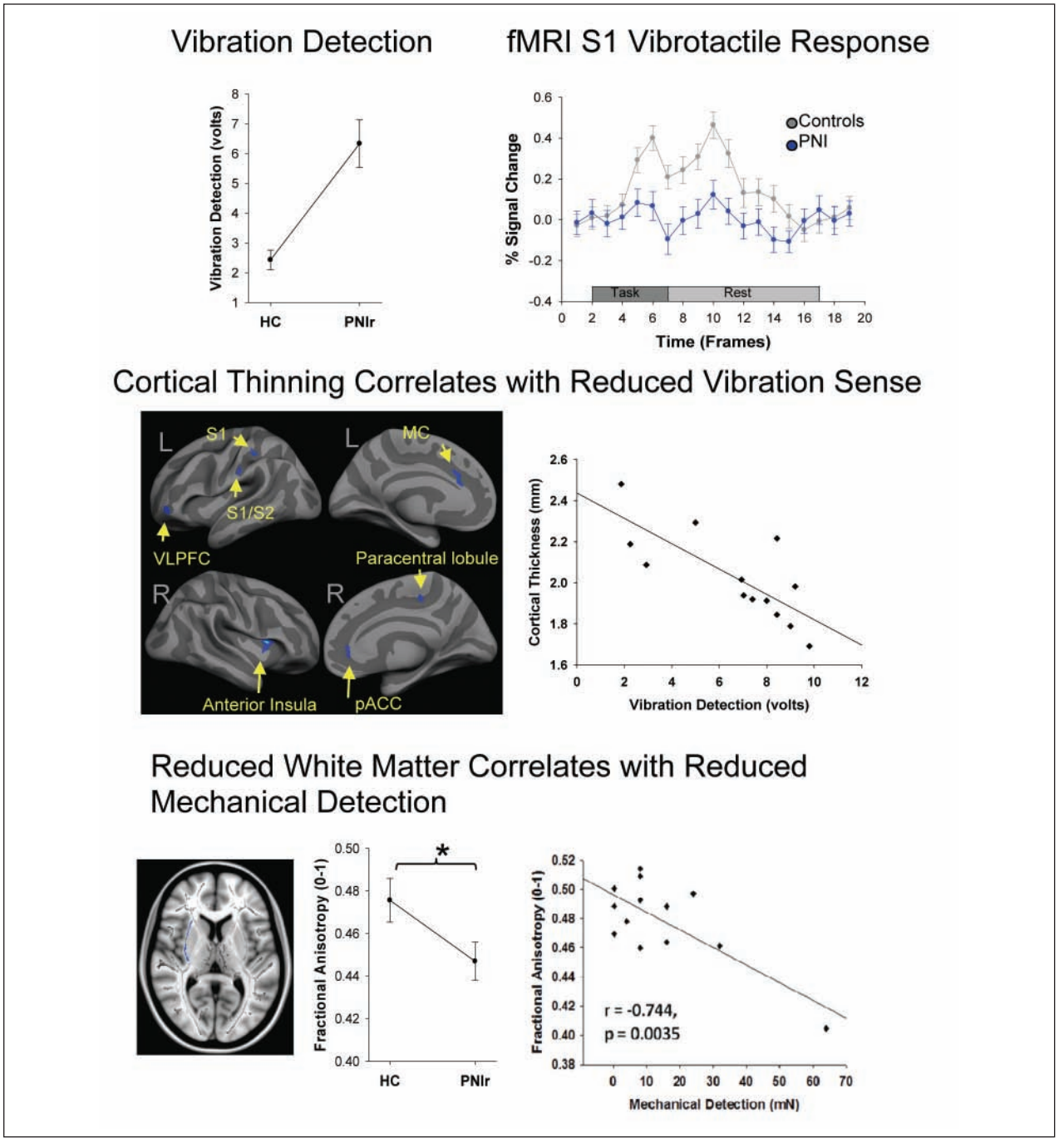


Figure 3. Brain plasticity and behavioral deficits following peripheral nerve injury and repair (PNIr). *Top panel:* Following PNIr, patients have reduced vibration detection and attenuated fMRI responses to vibrotactile stimuli within the somatosensory cortex (S1). *Middle panel:* The patients' reduced vibration sense was correlated with cortical thinning in several sensorimotor areas. *Bottom panel:* Reduced detection of mechanical stimuli was also correlated with lower fractional anisotropy in the white matter adjacent to the insula. HC = healthy control; PNI = peripheral nerve injury; VLPFC = ventrolateral prefrontal cortex; MC = middle cingulate cortex; pACC = pregenual anterior cingulate cortex. Modified with permission from Taylor and others (2009).

Furthermore, the patients showed cortical thinning in somatosensory (S1, S2), cingulate, and insula cortices and reduced white matter FA adjacent to the right insula. Importantly, the degree of structural deficits in S1 and insula corresponded with the degree of sensory detection loss. Taken together, these findings indicate that PNI can

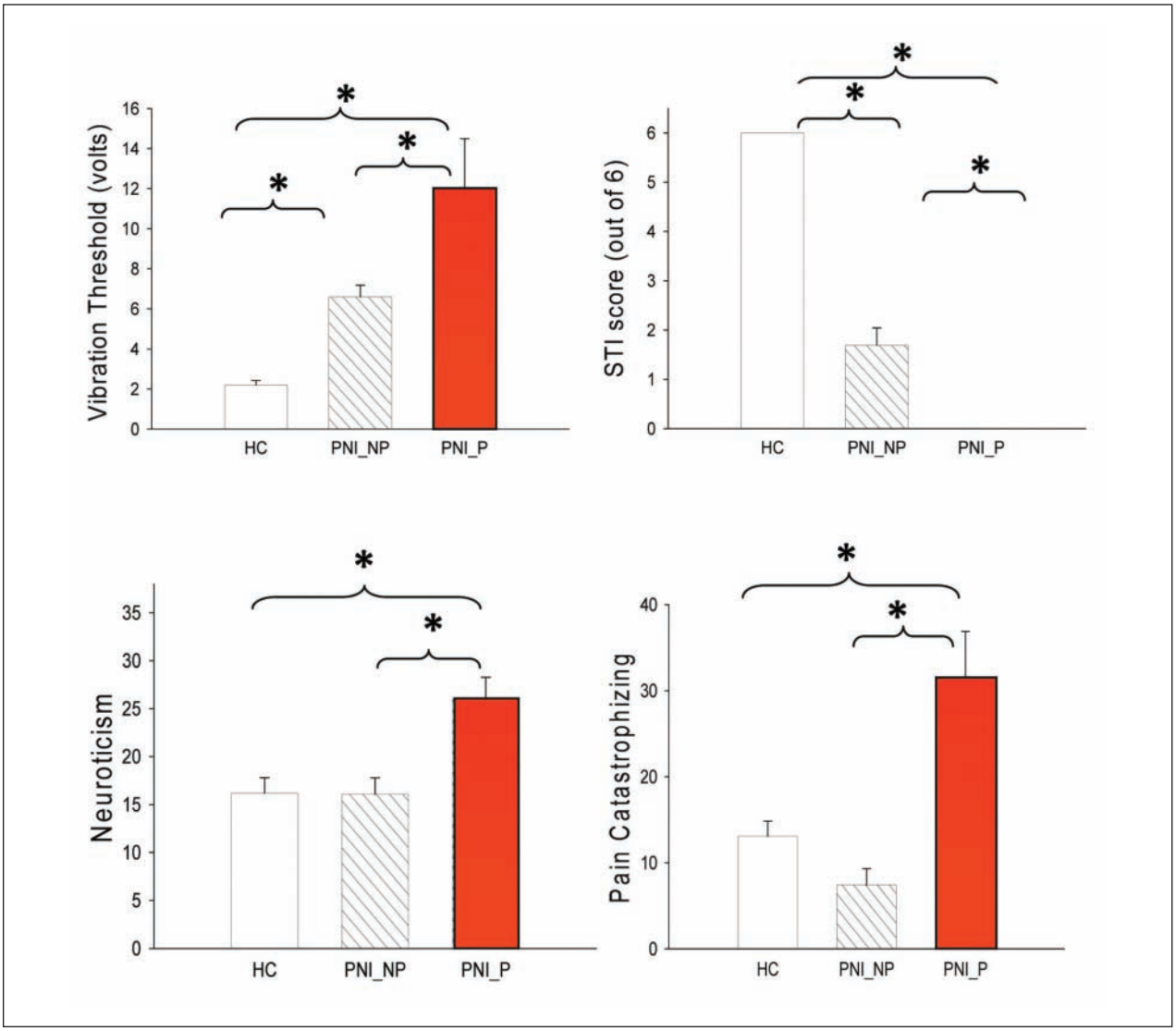


Figure 4. Sensorimotor deficits in patients with surgically repaired peripheral nerve injuries (PNIs) are more severe in those patients who developed chronic pain (PNI_P) than in those who did not develop chronic pain (PNI_NP). The chronic pain patients exhibited greater neuroticism and pain catastrophizing than the patients who did not develop pain. STI = shape texture identification; HC = healthy control. * significance at $P < 0.05$. Modified with permission from Taylor and others (2010).

lead to profound brain plasticity linked to sensory deficits, possibly via an A-β related mechanism (see Fig. 5).

The patients just described did not exhibit chronic pain. However, we have also studied another group of nerve-injured patients who had undergone identical surgical repair. These pain patients showed the same constellation of abnormalities as the nonpain patients but with greater severity and also had increased pain sensitivity to cold stimuli. Furthermore, these chronic pain patients had increased neuroticism and pain catastrophizing scores compared with the nonpain patients and healthy controls (see Fig. 4). These findings suggest that preexisting personality features may contribute to poor recovery. However, because these scores were obtained several years after nerve injury, it is possible that pain and sensorimotor loss early after PNI contribute to poor surgery outcome and the high personality scores, although neuroticism is thought to be stable across the lifetime. Regardless, a possible mechanism of the outcomes of PNI in the pain patients is shown in Figure 5.

Interestingly, recent studies have reported brain plasticity due to injury or pain that appeared to reverse following successful surgical treatment of the pain (Gwilym and others 2010; Rodriguez-Raecke and others 2009). These types of studies demonstrate the potential "plasticity of

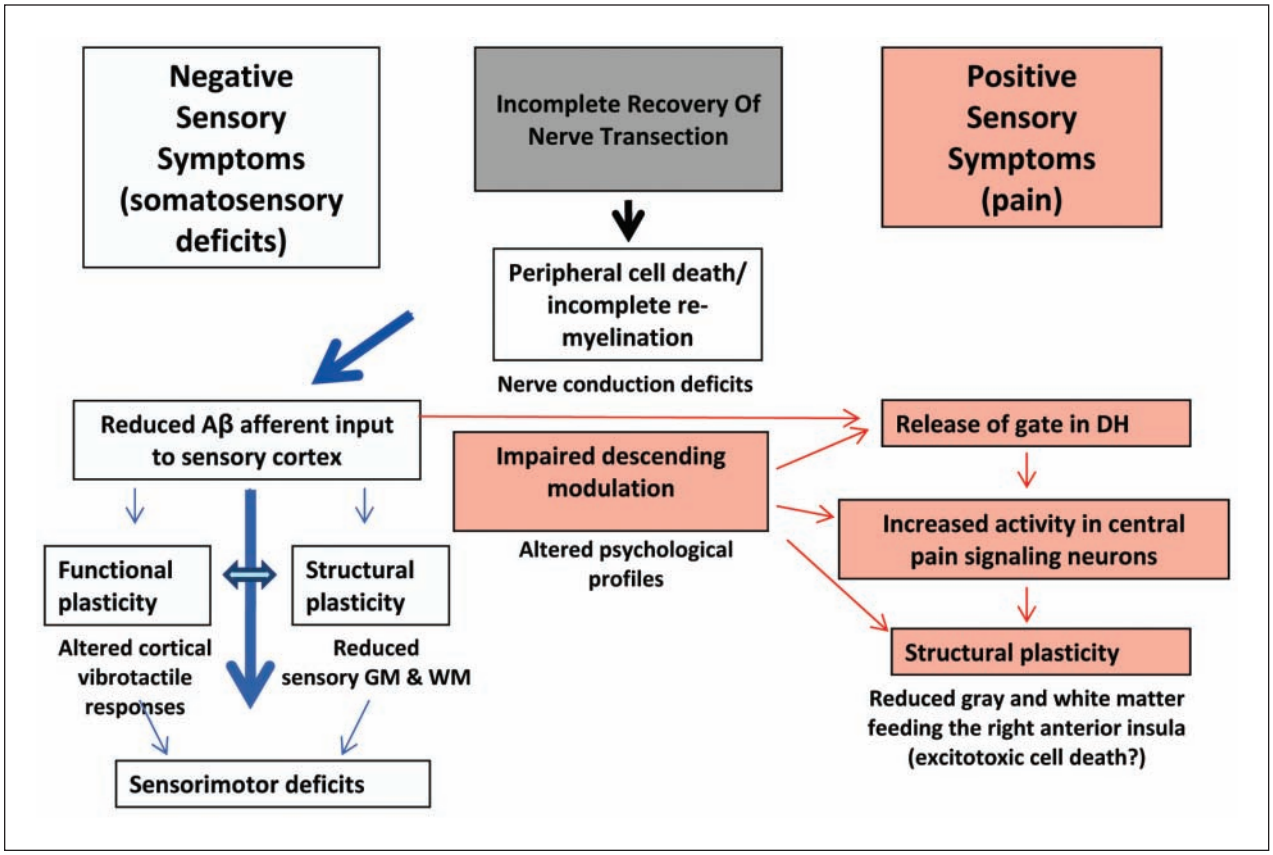


Figure 5. A model of the consequences of peripheral nerve injury to account for both somatosensory deficits and chronic pain. The model incorporates peripheral and central plasticity. DH = dorsal horn; GM = gray matter; WM = white matter.

plasticity" and provide enthusiasm for future therapies for a variety of brain abnormalities.

Conclusion and Future Directions

This review establishes that profound brain plasticity occurs after nerve injury in humans and that some of these changes reflect behavioral outcomes. However, recent evidence suggests that individual factors can contribute to the consequences of nerve injury and possibly trigger a maladaptive versus adaptive outcome. Future studies are needed to fully understand the interplay of individual factors such as personality with brain plasticity and potentially develop individually tailored surgical approaches and rehabilitation.

Declaration of Conflicting Interests

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