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# Plasticity in the Brain after a Traumatic Brachial Plexus Injury in Adults

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## Abstract

In this chapter, we aim to discuss the neurophysiological basis of the brain reorganization (also called plasticity) that associates with a traumatic brachial plexus injury (TBPI), as well as following the brachial plexus surgical reconstruction and its physical rehabilitation. We start by reviewing core aspects of plasticity following peripheral injuries such as amputation and TBPI as well as those associated with chronic pain conditions. Then, we present recent results collected by our team centered on physiological measurements of plasticity after TBPI. Finally, we discuss that an important limitation in the field is the lack of systematic measurement of TBPI clinical features. We finish by proposing possible future venues in the domain of brain plasticity following a TBPI.

**Keywords:** cortical plasticity, traumatic brachial plexus injury, peripheral lesions, sensorimotor cortex, rehabilitation

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## 1. Introduction

For a long time, synaptic networks in the brain were thought to be defined at birth and throughout the first years of life, remaining unchanged thereafter. However, contemporary research has shown that changes in functional brain organization do occur throughout an individual's life: synapses and dendritic budding are formed and eliminated, their efficacy being modulated through a complex network of neuronal interactions (reviewed in [1, 2]).

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The term “plasticity” refers to the capacity for such changes [3, 4] occurring in response to injury, learning, training, illness or therapy [5]. Plasticity has been since then considered as an intrinsic property of the human brain, fundamental for overcoming genetic constraints and adapting to environmental pressures, physiological changes and new experiences [6].

Brain plasticity that follows a peripheral nervous system injury has been extensively documented at molecular, synaptic and systemic levels both in animal models and in humans. These plastic changes are, however, still documented at a purely descriptive level, and the search for conceptual models that allow predicting the direction of these changes is becoming mandatory [7]. Moreover, from a clinical point of view, the demonstration that the plasticity phenomenon underlies robust functional gain is necessary [5]. Progress in this direction should guide the development of new therapeutic interventions. This chapter starts with a brief introduction on brain plasticity after peripheral lesions with a special case for brachial plexus injury. We shall then discuss the available evidence of functional recuperation after surgery and physical therapy. Finally, we will point on new directions toward a fresh approach to changes in the brain following a peripheral nerve injury.

## 2. Brain plasticity

### 2.1. Brain plasticity after a peripheral injury

It is now widely demonstrated that lesions on the periphery of the body are capable of promoting structural and functional modification in the sensory (S1) and motor (M1) primary cortices [8, 9]. In animal models, these changes have been shown to translate into the topographic rearrangement of the body representation [10–13]. In patients who suffered traumatic amputation of a limb, noninvasive studies using the transcranial magnetic stimulation (TMS) technique showed that reorganizations in M1 are characterized by an expansion of the motor representation of the stump toward that of the segment of the amputated limb and, more rarely, an expansion of the face toward the amputated hand [14, 15]. Similarly, the analysis of the somatosensory reorganization resulting from amputation evidenced an extension of the face-to-hand representation in the primary somatosensory cortex [16] and more rarely, from the shoulder toward the hand [17], and from the trunk toward the hand [18]. However, recent results in these patients [19, 20] have shed doubt on the existence of face-to-hand expansion, suggesting instead that the territory of the missing hand is little, if so, invaded by neighboring representations after an amputation. In fact, it is possible to retrieve from stump muscles an EMG activity related specifically to the voluntarily evoked phantom hand movements [21], suggesting that the hand motor commands are preserved in the brain (reviewed in [22]). Furthermore, hand transplantation is capable of reversing the amputation-induced reorganization, with the intrinsic muscles of the donor hand being represented in M1 of the patients who received the transplant [23]. Cortical reorganization of intrinsic hand muscles was also verified in patients with leprosy affected by ulnar and median nerve injury [24]. Taken together, these results suggest that the sensorimotor representations in the brain are highly Mutable, that the hand representation persists in the sensorimotor cortex after an amputation and finally, that the changes following a peripheral lesion are reversible.

The mechanisms that underlie the occurrence of these plastic dynamics in the brain after injury and surgical reconstruction in the periphery of the body are still largely unknown and thus under active investigation. Different explanations such as neuronal budding and the unmasking of previously existing synapses, kept functionally silent by inhibitory gabaergic cortical circuits, are not mutually exclusive and should be taken into consideration [25, 26]. It is also possible that part of the observed reorganization is arising from subcortical plasticity and not only by new cortical–cortical projections [27, 28]. Furthermore, depending on the type of deafferentation, the mechanisms involved in the reorganization of the cortex might be different and could occur simultaneously at different levels of the sensorimotor system [27, 28].

## 2.2. Brain plasticity and pain

The phantom limb is a well-described phenomenon relating brain plasticity and limb amputation. When a persistent limb sensation occurs in the form of pain, the phenomenon is described as phantom limb pain [29]. Phantom pain has been shown to correlate with the degree of cortical reorganization [30, 31]. Using functional MRI, Lotze et al. [32] found a displacement of the cortical representation of the lips in M1 and S1 toward the representation of the hand in amputees, with a positive correlation between the displacement degree and the intensity of phantom pain. Furthermore, the imagined movement of the phantom hand activated the neighboring face area in the patients with phantom limb pain but not in the pain-free amputees. These data suggest selective coactivation of the cortical hand and mouth areas in patients with phantom limb pain [32].

The idea that cortical reorganization plays an important role in the pathophysiology of pain and that pain would lead to cortical reorganization has been confronted by the proposition that the plasticity generated by the phantom pain results both from the maintenance of the local cortical representations of the amputated limb and the disturbance of the interregional connectivity in the primary sensorimotor cortex [33]. However, it is possible that both processes (reorganization and preservation of limb function) occur simultaneously. Furthermore, the impact of peripheral factors such as afferent stimuli from the residual limb might be considered as an additional component in the pathology of phantom pain [34]. Besides, different experimental contexts, different methods for evaluation of cortical reorganization, and the difficulty in considering the impacts of psychological effects of the lesion seem to play an important explanatory role when one considers the variety of results in this domain, thus calling for the need to continue exploring this phenomenon [34].

Functional reorganization was also detected in pain syndromes. Flor et al. [35] investigated S1 reorganization in patients with chronic low back pain and observed a shift of the cortical representation of the back, interpreted as an expansion of the back's representation into the foot and leg area. Furthermore, Apkarian et al. [36] demonstrated that cortical gray matter density decreases regionally in chronic back pain patients. Other studies have also reported similar brain morphological changes related to various chronic pain conditions such as complex regional pain syndrome [37], chronic headache [38], and fibromyalgia [39]. The Apkarian group, in a series of revisions, further proposes that the transition from acute to chronic pain would be due to learning mechanisms within the cortical–limbic circuitry, leading to the formation of continuously reinforced memories that could not be extinguished, as

a consequence of motivational and emotional associations with the painful stimuli, possibly potentiated by a greater learning capacity due to a predisposition to addictive behavior [40].

### **2.3. A model for brain plasticity investigation: brachial plexus injury**

The brachial plexus (PB) is composed of a set of peripheral nerves responsible for the sensory, motor and autonomic innervation of the upper limb. Injury to peripheral nerve structures and/or medullary avulsion as a result of a traumatic brachial plexus injury (TBPI) lead to changes in cortical representations [41–44] and are also often associated with neuropathic pain [45]. Surgical procedures have been used in the treatment of TBPI patients with a view to the partial reconstruction of the lost innervation [46]. In particular, the nerve transfer technique (neurotization) has been described as effective for restoring denervated muscle function, particularly in cases where spinal root avulsions are involved [47]. However, the complete reconstruction of the motor bundles that innervate the arm after a TBPI is still not possible and priorities have been established to guide reconstructive strategies, the rescue of elbow flexion being the main purpose of the more prevalent surgical procedures [48–50]. As an important surgical outcome, Htut et al. [51] showed that pain reduction was greater for the group of patients who underwent grafting and nerve transfer and that pain intensity was lower for the group of patients submitted to surgery than for those who did not undergo the procedure.

Mano et al. [41] and Malessy et al. [42] were pioneers in the study of cortical plasticity in patients with TBPI employing transcranial magnetic stimulation. Since then, a few studies have been published in order to evaluate these plastic phenomena. After surgical transfer of the intercostal to the musculocutaneous nerve, a shift from medial to lateral of the biceps representation in M1 cortical map was reported [41, 43]. However, after this surgical procedure the tactile stimulation of the newly innervated forelimb skin area often results in tactile sensation in the chest region [52–54]. The neurotization of the biceps with fibers from the contralateral C7 root is another possible strategy to rescue elbow flexion. C7 root fibers are normally involved in adduction and extension of the ipsilateral arm. With this neurotization, flexion of the injured arm will no longer be under the control of the contralateral hemisphere, but rather under the control of the ipsilateral hemisphere. The cerebral hemisphere ipsilateral to the injured plexus will be controlling both the extension of the intact arm and flexion of the neurotized arm. In a fMRI study, performing an elbow flexion after the contralateral C7 neurotization of the biceps resulted in a bilateral cortical activity in a network comprising the premotor and primary motor cortex as well as the posterior parietal and supplementary motor areas ipsilateral to the neurotized arm [44].

In a fMRI longitudinal study, Yoshikawa et al. [55] accompanied 20 TBPI patients before and up to 32 months after different TBPI surgeries. Patients were asked to perform or simulate flexion/extension elbow movements with the affected arm. A reduction in the elbow movements representation in the contralateral sensorimotor cortex was observed at approximately 3 months after injury, reducing further after 1 year of injury (9 months of surgery). Over time, as the functional recovery of the elbow movements occurred, a concurrent reemergence of the activation areas was observed in the sensorimotor cortex.

Employing resting state fMRI Fraiman et al. [56] analyzed the empirical functional correlations between neighboring voxels. They found evidence of faster correlation decay as a function of distance in the M1 region corresponding to the upper limb but not in the face area in patients with TBPI as compared to a control group. A possible mechanism to explain the lowered correlation between neighboring voxels as compared to control subjects would be due to reduced activity in the intrinsic horizontal network, which is thought to orchestrate motor synergies in M1. Interestingly, these modifications also encompassed the M1 trunk/lower limb representation, suggesting that TBPI might imply in a bodily extended motor dysfunction. Accordingly, it was also found that TBPI affects body balance [57]. Souza et al. [57] showed that TBPI patients oscillate more in the sagittal plane as compared to a control group while standing barefoot on a force platform for 60s.

Liu et al. [58] and Hsieh et al. [59] explored changes in interhemispheric functional connectivity, observing decreased connectivity and loss of cortical inhibition between the primary motor areas of the two hemispheres after TBPI. Fraiman et al. [56] also found faster correlation decay as a function of distance in ipsilateral M1. Lu et al. [60], using voxel-based morphometry in fMRI, found less gray matter in BPI patients in brain regions such as the cerebellum, the anterior cingulate cortex, the bilateral inferior, medial and superior frontal lobes and bilateral insula, most regions closely related to motor functions. The authors speculate that this loss of gray matter might be the neural basis for the difficulties in motor rehabilitation of BPI patients. Other studies have explored further aspects of cortical plasticity after TBPI. Employing resting-state fMRI, Feng et al. [61] investigated differences between right and left injuries in right handed individuals revealing that right limb injuries induce greater cortical reorganization. Moreover, plasticity does not seem to be restricted to the sensorimotor cortex, involving higher-order regions such as the precuneus, the lateral aspect of the posterior parietal cortex, the superior parietal lobe, and the intraparietal sulcus [62]. Taken together, these results call for a more careful evaluation of the functional loss after TBPI.

Socolovsky et al. [63] recently reviewed different factors that could play a role in neuroplasticity and functional regeneration after nerve transfer. Distance between cortical territories of the donor and receptor nerves, the presence of preexisting brain connections, gross versus fine movement restoration, rehabilitation, brain trauma and age at lesion were listed as influencing functional restoration [63].

Rangel [64] employed an action observation and electroencephalogram (EEG) paradigm to investigate if a TBPI affects the capacity to anticipate the occurrence of sensory and motor events in the space around the arm. If it was the case, a change in the neural signature specific to each context (observation of a hand movement or of a hand about to be touched by an external object) might be verified. Preliminary results showed that the electrophysiological marker associated to predicting actions was preserved in the left sensorimotor region when TBPI patients with incomplete lesions sparing the hand observed actions performed by a right hand. Crucially, the ability to estimate upcoming touch events in the hand was preserved only for the sensorimotor cortex contralateral to the spared limb, suggesting a dependency of online sensory information to estimate events around the hand.

## 2.4. Clinical impact of TBPI

Although cortical plasticity after TBPI and its reconstruction has already been widely demonstrated [41–44, 46, 55, 56, 58, 59, 61–63], it is still very challenging to evaluate its clinical impact. Below we speculate about some reasons for that fact.

The first reason is that TBPI outcomes are still underestimated. It is known that TBPI consequences go beyond motor disability and pain. It also includes psychic, social and quality of life impairment [65, 66]. Since TBPIs are complex and heterogeneous, it is not expected that a single measure should completely cover all these aspects [67]. However, TBPI outcome reports are routinely limited to motor function, specially muscle strength, most frequently measured through British Medical Research Council (BMRC or MRC) scale [68]. Notwithstanding, TBPI may lead to limitations in various daily living activities such as washing, dressing, combing, eating, and preparing meals, in addition to restricting social participation, such as work, hanging out with friends and practicing sports. All this can have a strong impact on the individual's lifestyle [69, 70]. A cohort study followed 629 polytraumatized patients to evaluate the influence of upper extremity trauma on in-hospital progress, rehabilitation and social situation in the long term. The subgroup with TBPI presented slightly worse scores on mental and physical components of the quality of life survey SF-12 and significantly worse results in the score used to classify the rehabilitation status, which included a self-assessment of individual, social, financial, professional and medical items and a questionnaire and examination performed by the surgeon. Furthermore, the average duration of rehabilitation was more than twice as long, there were significantly longer duration of unemployment and higher retraining rate for TBPI patients when compared to other injuries [71]. Besides, there is a gap regarding the assessment of activities and social participation post-TBPI [72]. In a recent systematic review, Hill et al. [69] found that upper limb activities are rarely evaluated for this population, and there is still a shortage of clinimetric evidence in the questionnaires used to assess activity after TBPI. As a consequence, the major cortical plasticity measures take only motor function and their brain-related changes as their outcomes. It is possible that nonmotor consequences of TBPI also result from cortical plasticity driven by mechanisms still unrecognized and unexplored. This knowledge may open new doors to access and understand cortical plasticity.

Another reason lies on the research protocols to evaluate cortical plasticity after a TBPI. Many factors that may also influence cortical plasticity are frequently disconsidered, for example: dominance [41, 43, 59], side of injury [58], cause of injury [55, 59, 61], associated traumas [41–44, 55], physical therapy treatment [42–44, 55, 56, 59, 61] and pain relief medication [41–44, 55, 56, 59, 61]. Several factors influence the execution of activities by the upper limb, besides hand dominance. Some activities require unimanual and others, bimanual skill [73]. Furthermore, individuals with TBPI can adapt to their injury over time, performing tasks with their unaffected limb, changing handedness or compensating by using other body parts [74]. In addition, it is known that tasks performed by the upper limbs are complex, requiring control of positioning and multiple joints in varying degrees of freedom [75, 76]. This situation prevents the translation of experimental evidence into useful tools in clinical practice.

## 2.5. TBPI rehabilitation impact on cortical plasticity

A better understanding of cortical plasticity in TBPI may improve patients outcomes through the development of more accurate prognostic measures and more effective and customized therapies. Surgical treatments such as nerve, muscle and tendon transfers require plasticity to have good results (reviewed in [63]); therefore, after surgical treatment, specific approaches should be performed according to the type of surgery to which the patient was submitted. For example, in neurotization or nerve transfer, physical therapy should involve muscles related to the donor's nerve [43, 77–79]. The patient initially performs movements of the target muscle through the activation of the donor nerve muscles and this synergism will be useful in the beginning of the treatment to gain strength at the target muscle. Recently, Dahlin et al. [79] reported a case of a TBPI patient, who was initially treated with a transfer of intercostal to musculocutaneous nerve. Due to insufficient recovery of elbow flexion, after 2 years, he received a gracilis muscle transfer reinnervated by a phrenic nerve transfer. Electromyographic measurement showed that different activation patterns of the biceps and gracilis muscles were evoked by coughing and deep breathing, respectively. Moreover, voluntary elbow flexion elicited activity in the biceps and gracilis muscles associated with a decreased activity in intercostal muscles. These results corroborate findings [41, 43] indicating that the neural control of elbow flexion in M1 gradually separates from the control of voluntary breathing. In addition, it brings important information for elaborating therapy protocols concerning which specific task would be encouraged in order to facilitate elbow flexion (i.e., transferring coughing function in patients operated with intercostal nerve transfer and transferring deep breathing function in case of phrenic nerve transfer).

Moreover, Souza et al. [57] showed that motor impairment after TBPI is not restricted to the upper limb segment, since the clinical balance assessment and posturographic analysis in a TBPI group indicate that these individuals do exhibit balance impairments. This study indicated that rehabilitation after TBPI should not be directed only to the upper limb, but also to prevent and treat the secondary outcomes of this condition.

The TBPI rehabilitation team, therefore, must have a good understanding of the cerebral changes caused by the injury, the surgical reconstruction and the physical therapy, so that an individually tailored rehabilitation program can be applied according to the injury characteristics and the functional problems experienced by the patient in order to guide plasticity so that the best possible clinical outcome can be achieved [79]. Many TBPI rehabilitation programs are purely empirical, but recent studies have suggested that specific interventions could accelerate axon regeneration and brain plasticity [80, 81]. There is accumulating evidence that central adaptation factors are relevant to the recovery following peripheral trauma, which may also contribute to optimal functional outcomes. The modulation of the central nervous system is a key component of current rehabilitation strategies, being it sensory re-education, constraint induced movement therapy, exercise, electrical stimulation or transcranial stimulation [82]. Further studies investigating brain plasticity following TBPI rehabilitation with a longitudinal design are needed to a better understanding of the natural history of the disease, the cerebral response to the injury and changes following rehabilitation through the potential approach of guided plasticity.

## 2.6. Relevance

Improving knowledge on TBPI and its treatment is also an opportunity to reduce its social and economic impacts, the main victims being in general male in working age. Since Narakas' report in 1985 [50], subsequent series on brachial plexus injury around the world reaffirmed the importance of motor vehicle accidents, especially motorcycle, as its main cause [83–89]. The same trend is observed in series covering peripheral nerve injury in general [90–93].

However, traffic accidents as a whole, including motorcycle ones, impact more intensely in developing countries [94]. As an example of this situation, in Brazil, a huge increase by 400% in motorcycle fleet was observed from 2003 to 2015 [95]. In recent years, there grew up from 20 million in 2012 to more than 25 million in 2017 [96]. A consequent increase in motorcycle accidents reports should be naturally expected. However, official data show that the relative contribution to traffic accidents by motorcycle is much higher than could be previously imagined. In the first 6 months of 2017, motorcycles represented 27% of total Brazilian vehicular fleet, but were responsible for 74% of total indemnity paid by traffic accidents in the same period. Since traffic accidents involving motorcycles represent the most frequent cause of TBPI [83–89], an increase in TBPI in the Brazil, and in other developing countries, can be predicted in the near future.

## 3. Conclusions

There is mounting evidence that the brain is capable of recognizing and incorporating new information after a peripheral lesion followed by its surgical reconstruction. Frequently, these plastic processes are associated with persisting pain, a phenomenon that has been shown to correlate with the degree of cortical reorganization. However, the mechanisms underlying these phenomena are still only partially uncovered. TBPI is an interesting model of brain plasticity due to its incidence, the large variety of injury levels and the available surgical reconstructive procedures. For instance, studies with TBPI have shown changes in cortical representation after surgical transfer. Shortcomings in interpreting the results from studies relating brain changes after TBPI and its reconstruction are the paucity of systematic correlation of TBPI with detailed clinical evaluation protocols and the need of further investigation of physical therapy outcomes after TBPI. New venues in this domain shall be opened through the development of approaches allowing putting together more detailed clinical investigation protocols and that of brain mechanisms associated to plasticity after TBPI.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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