The underlying goals of brain and spinal cord surgery are generally to 1) decompress nervous tissue (i.e., to treat trauma, tumors, degenerative processes, and infections), 2) maintain or restore circulation (vascular surgery), and 3) resect or otherwise stimulate areas that interfere with normal function (functional neurosurgery). In contrast to brain and spinal cord injury, damaged nerves can be repaired surgically based on axons’ capacity to grow after being sectioned. The restoration of neurological function after these procedures is primarily attributable to the direct effects of surgery, often times aided by the process of neuroplasticity. This term refers to the CNS’s ability to reorganize and adapt to internal changes or environmental stimuli and thereby optimize functional outcome.

The term “brain plasticity,” although popular, limits such plasticity to the brain while ignoring other changes that occur in the spinal cord.

Plasticity is not linked only to pathological scenarios. For example, learning new repetitive motor skills is also associated with neuroplasticity. In a study of primates specifically trained to use a single finger to perform a specific task, the researchers documented expansion of the motor cortical representation of that finger and diminution of the motor cortical representation of the remaining fingers of the same hand. Motor skill training enhances plastic changes in the CNS, something that does not happen when enhanced strength is the only goal of training.31

Neurosurgeons require some level of understanding of...
neuroplasticity to plan their surgeries. For instance, modern techniques for brain tumor resection in eloquent areas include the precise localization of each function via brain mapping. Eloquent zones must be preserved during surgery with the patient awake. Moreover, if an eloquent area is affected by a slow-growing tumor, experienced neurosurgeons generally avoid resecting that part of the tumor. It is well established that tumor progression in the years thereafter will diminish the functional importance of the area significantly, which will enable a safer resection of the expanded tumor later.12,58

Not all plasticity-related changes should be automatically considered beneficial. For instance, both deafferentation pain after severe brachial plexus injury (BPI) with root avulsions and phantom limb pain after an amputation are linked to maladaptive processes mediated by plasticity.8,39,53 These pain stages are linked to the creation of a “black hole” in brain sensory zones that no longer receive afferent information.

Severe peripheral nerve lesions and severe BPI result in a complete loss of afferent and efferent input to the CNS, which thereby produces a number of important changes in the CNS. Some of these changes occur immediately after the injury.38,66 and many of them expand beyond the somatomotor cortex.15,37 The trigger for brain reorganization is deafferentation. In fact, much of what we know about plasticity stems from studies conducted in amputees, in whom the original hand motor cortex is “invaded” by plasticity zones significantly, which will enable a safer resection of the expanded tumor later.12,58

The main objective of this article is to link the outcome of nerve transfers, applied predominantly in surgery for the treatment of BPI, in view of our current understanding of brain plasticity.

**Intercostal or Phrenic Nerve Transfer to the Musculocutaneous Nerve for Elbow Flexion**

Brain plasticity after intercostal-to-musculocutaneous nerve (ICN-MCN) transfer in surgery on the brachial plexus has been studied the most extensively. At the beginning of recovery, patients who have undergone this nerve transfer generally exhibit involuntary contraction of the biceps that is linked to breathing. After a short period of time, patients become aware that they can contract their biceps, but only by sustained inspiration or expiration. However, contraction (and the maintenance of elbow flexion) ultimately becomes independent of respiration. Flexion then can be maintained while the patient breathes normally. Complete independence between the 2 functions, however, is never actually achieved.43

In plasticity studies, researchers have found that after ICN-MCN transfers, flexion is initially controlled by the sagittal region of the primary motor cortex.43 This area is related to the intercostal muscles active in respiration (Fig. 1 left). After a few months, however, the original more laterally located area for voluntary biceps control becomes involved (Fig. 1 right). This shift in cortical activity from medial to lateral is most likely based on the activation of a preexisting interneuronal network with low-activity connections between the 2 involved cortical areas (Fig. 2).

Intercostal muscles contract simultaneously with the biceps when, for instance, a heavy object is lifted. This movement, after all, requires not only biceps contraction but also, although less obvious, stabilization of the thorax and torso posture.

From these studies it was concluded that to achieve successful voluntary control after nerve transfer, the donor and acceptor must have some connection between the 2 motor areas (i.e., horizontal intrinsic connections) before transfer.22 These central connections are activated by peripheral nerve transfers, which thereby induce plastic changes in the cortex.

Similar changes from breathing-related control to voluntary flexion independent from breathing can be observed after a phrenic nerve–MCN transfer, with which the same clinical progression (starting with respiration-controlled arm movement, followed by voluntary control of elbow flexion) is seen. The reported results of phrenic nerve–MCN transfers are comparable to, and in some cases better than, those of ICN-MCN transfers,36,56 which might have several explanations, including the greater number of axons that the phrenic nerve has relative to ICNs (Fig. 3).

**Hypoglossal Nerve as Donor to the MCN or Facial Nerve**

Good biceps muscle strength can be obtained with a hypoglossal nerve–MCN transfer.42 The functional outcome, however, is poor, because independent voluntary control over the reinnervated muscle is not restored. To control the biceps muscle to flex the elbow, the tongue has to be pushed against the hard palate. As soon as the tongue is relaxed, the biceps muscle also relaxes. Talking or chewing evokes involuntary biceps contractions, which cause the arm to move involuntarily. In contrast, good results (House-Brackmann Grade III28) can be expected after a hypoglossal nerve–facial nerve transfer.24,26,49,57 One possible explanation for this discrepancy is that no connection between elbow flexion and the tongue cortical area exists (Fig. 4), whereas good horizontal connections between the tongue and the face area do exist (Fig. 5).

However, a final House-Brackmann grade of III after a hypoglossal nerve–facial nerve transfer implies good symmetry at rest and normal talking. If facial emotional movements (e.g., crying or laughing) are involved, asymmetry reappears, which is probably because no horizontal connections between emotion-controlled movements (which originate from different zones of the brain) and the hypoglossal cortex exist. In this case, as in many others, complete functional adaptation mediated by plastic changes has its limits.

**Contralateral C-7 Transfer**

The contralateral C-7 transfer technique can be used
Neuroplasticity is an influential factor in nerve transfers to treat severe BPI with root avulsions. In this technique, the spinal nerve C-7 from the healthy arm is transferred partially or completely to a target nerve in the affected upper limb. The literature on contralateral C-7 transfers was reviewed recently, and the results were not as excellent as originally believed. Indeed, to move the affected limb, they have to flex their healthy arm to initiate muscle contraction in the reinnervated limb.

A functional MRI study revealed that bilateral activation of the motor cortex occurs during movement of the reinnervated arm. The original motor area for flexion of the arm is still involved but in concert with the ipsilateral cortex, which normally is not the case. This process is mediated by bilateral premotor and primary motor connections, which provides an explanation for the main drawback of this technique, namely, that very few patients regain independent movement control. Indeed, to move the affected limb, they have to flex their healthy arm to initiate muscle contraction in the reinnervated limb.

One case study is of particular interest with respect to interhemispheric connections. A woman who suffered an amputation of her right arm above the elbow and who also had complete avulsion of the left brachial plexus underwent reconstructive surgery. The right brachial plexus was connected to the left brachial plexus by interposing grafts, and she recovered several movements in her left arm. However, to effect these movements, she had to think about flexing her phantom right arm. It is interesting that on functional MRI, signals were detected bilaterally in the thalamus, caudate, insula, and sensorimotor cortex during any elbow-flexion task.

**Plasticity in Distal Nerve Transfers in Relation to Adjacency of Motor Areas**

The transfer of a nerve fascicle of the ulnar nerve to a biceps branch (the Oberlin procedure) was popularized in 1994. This technique changed brachial plexus surgery profoundly. First considered a “salvage procedure” for use when roots are avulsed and not available for grafting, the procedure has transformed over the years into a first-line procedure for biceps reinnervation in adults and is being increasingly used in children. One big reason for the popularity of the so-called Oberlin procedure is the high success rate of 90% or greater. One variation in the original technique, which increases the number of axons reaching the agonist target muscles (e.g., double transfers...
from ulnar to biceps and median to brachialis nerves) has generated even better results; between 95% and 99% of patients experience a good result. Other distal nerve transfers based on this concept (e.g., triceps branch–axillary nerve transfer [so-called Somsak procedure] \(^33,62\) and wrist and finger extension branch–triceps branch transfer \(^18\)) have also been associated with very high success rates.

The success of Oberlin’s nerve transfer is based on the short distance that the outgrowing axon has to cross. Because the transfer is performed distally, the distance to the target muscle is no more than a few centimeters, which explains why muscle reinnervation occurs much faster. \(^23\) In addition, successful distal transfers illustrate the 2 core principles of neuroplasticity that determine good results: 1) the donor and acceptor cortical regions share the same motor control pathways and 2) previous connections between the 2 areas exist (Figs. 7 and 8). It can be speculated that not only the short distance to the target muscles but also the good conditions for plasticity explain the high rates of success of distal nerve transfers.

One patient who recently underwent the Oberlin procedure was compared with a control individual. The authors found that the areas and peaks of activation were quite similar. These findings provide additional support for the role of plasticity in attaining the excellent results that distal nerve transfers generally achieve.\(^30\)

Reinnervation of Hand Movement: Is It Just a Problem of Target Distance?

The results of hand reinnervation after BPI in adults have been poor. The classic explanation is the long distance that axons have to elongate to reach their distal muscle targets. Although this distance is unquestionably a factor, additional issues regarding neuroplasticity in relation to hand reinnervation control should be considered.\(^37\)

First, shoulder or elbow movements, which are gross, respond better to reinnervation than finer hand movements.\(^34,53\) Distal nerve transfers undertaken to reinnervate the hand (which eliminate the deleterious effects of long distance) with pure motor targets (which diminish axonal misrouting or dispersion) yield acceptable results for hand- and finger-grasping tasks. However, intrinsic muscles recover poorly, and fine movements that the normal human hand is able to perform are not recovered.

Second, in examining the extent of cortical representation of the hand (and especially the thumb) in the motor cortex, it is easy to understand that a BPI that affects the C-7, C-8, and T-1 roots produces extensive denerva-
Neuroplasticity is an influential factor in nerve transfers

It is unlikely that any surgical reinnervation will be adequately reparative (Fig. 9). The “black hole” that remains is so large because it is not possible at present to get enough axonal donors to fill it adequately.

Moreover, in both the published literature and our own experience, motor hand reinnervation does not produce good results in patients with complete brachial plexus palsy. Some isolated attempts at flexor reinnervation via phrenic nerve transfers, in special cases, yielded some recovery of finger flexion. However, the problem is not how forcefully the muscles move but how useful the movements are. Even with acceptable muscle contraction and finger flexion, such movement is not truly independent of breathing, as when innervating the elbow. Plastic changes in the cerebral cortex do not occur in these patients, because the connections between the hand and trunk are far from each other and the 2 areas do not share the same motor pathways (Fig. 10).

Reinnervation of Sensation

The intercostobrachialis nerve, a sensory nerve that supplies sensation to the skin of the thoracic wall and axilla, was used for transfer to the sensory component (lateral contribution) of the median nerve.21 A couple of years after the procedure, stimulating the median nerve territory of the injured hand was perceived by the patient but only in his axilla (L. Foroni, personal communication, 2016). This finding was predicted by one of the authors (M.M.) based on the following observation after ICN-MCN transfer. If the area of the lateral antebrachial cutaneous nerve is touched or stroked, patients locate sensation on the thoracic wall, even years after the ICN-MCN transfer. So, although voluntary motor control over the biceps is restored, it does not account for localization of sensation, which reveals that sensitive plasticity and motor plasticity do not follow the same pathways, as would be logical to presume. Even when a good result in terms of restoring protective sensation is attained, this example clearly reveals some of the limitations of neuroplasticity.

Effects of Brain Trauma

Contrary to humans and primates, rats were found to be unable to readapt function after a nerve transfer, even when the transfer was successful.6 Despite having electrophysiologically proven axonal continuity, rats cannot learn to move a certain target muscle after reinnervation. In all likelihood, the lack of effective brain plasticity in rats explains these findings. Can we link this knowledge to what happens in a severely injured human brain?

In fact, to our knowledge, the effect of traumatic brain damage on the success of peripheral nerve recovery has not been studied extensively in humans. It is our (M.S.)
clinical experience, however, that in patients with concomitant brain injury and BPI, the results of reconstructive brachial plexus surgery are worse than those in patients with isolated BPI, which might be a result of extensive injury to the white matter subcortical networks that are involved in brain plasticity (Fig. 11).

It is interesting to note that in a recently published report, it was shown that C-7 transfers promote locomotor recovery in rats even when they have a severely injured contralateral hemisphere.\(^{29}\) The corpus callosum, as the main connection between the 2 hemispheres at the cortical level, is the main pathway for this enhancement.

Precise knowledge about the effect of brain trauma on these mechanisms remains lacking. Until more is known, patients with concomitant brain injury and BPI should be considered cautiously as candidates for reconstructive brachial plexus surgery.

**Neonatal Brachial Plexus Palsy**

It has been demonstrated extensively that the results of nerve surgery to treat neonatal brachial plexus palsy (NBPP) are superior to those of surgery in adults with BPI because of the higher axonal regenerative capacity in infants.\(^{35,46}\) Even functional hand reinnervation can be obtained in patients with NBPP and is actually the first objective of reconstruction in those with complete palsy. The 2 main explanations for this success are that 1) the potential for axon growth is greater in young children, and 2) the distances from the repaired brachial plexus to the muscle targets are shorter.

Modern concepts of neuroplasticity can be superimposed on this existing knowledge. Although neuroplasticity is retained over one’s entire lifetime, it can be hypothesized that a young brain has a greater capacity for remodeling. In fact, it was shown recently in infants with right NBPP that hand dominance is located in the right hemisphere,\(^{16}\) which is also their language-dominant hemisphere.\(^3\)

As mentioned earlier, however, not all plasticity should be viewed in a positive light. In infants, there exists a phenomenon that has been called “developmental apraxia,” in which the muscles are weak and produce no effective movement of the limb as a result of early adverse plasticity associated with erroneous central motor programming. With neurophysiological and intraoperative stimulation, however, these same muscles exhibit good function and strength.\(^9\)

Another difference between infants and adults is that infants do not seem to develop neuropathic pain or phantom limb pain syndromes, as seen in adults.\(^{27}\) This difference is probably attributable to the extensive reinnervation that occurs in the young, which is contrary to the maladaptive response linked to partial reinnervation that commonly occurs in older children and adults.\(^{1,5}\)

Another interesting finding reported in the literature is that after nerve transection and repair the immature brain receives disorganized sensory input, just as happens in...
Neuroplasticity is an influential factor in nerve transfers

adults. However, at least among immature monkeys, it has been demonstrated that such jumbled input can be reorganized to successfully create a new somatotopy, which leads to good sensory outcomes.17 This finding correlates well with the relatively good sensory response found in children after nerve reconstruction compared with that in adults.13

Whatever the neurobiological background, these examples show the likelihood that neuroplasticity potential is more prominent after NBPP and might account partially for the good results obtained.

The Problem of Combined Agonist and Antagonist Muscle Innervation

Modern concepts of plasticity must be considered when performing simultaneous agonist and antagonist muscle reinnervation during surgery on the brachial plexus.

For instance, in a small series reported by Zheng et al.,67 simultaneous phrenic nerve transfer for elbow flexion and ICN transfer for elbow extension yielded very poor results for elbow extension but good results for elbow flexion. Because both the phrenic nerve and ICN are activated during inspiration, they could be considered agonistic muscles. The predominance of elbow flexion over extension in this series might be explained by the phrenic nerve being a more effective donor because it has more axons than do ICNs. It is assumed that the first muscle that is reinnervated (in this case, the biceps) initiates a cascade of brain reorganization, frustrating the successful regain of control over the antagonistic triceps. It is not known what would happen if donors were reversed; would the results for the triceps exceed those for the biceps?

In contrast with the results of Zheng et al.,67 good elbow reinnervation using the phrenic nerve was obtained in a recent series20 in which elbow extension also was attained successfully via a completely different donor (i.e., C-5 or C-6).

Another interesting finding that shows how impossible it is for the brain to innervate agonist and antagonist muscles simultaneously and successfully with the same donor can be found in a series report by Bertelli and Ghizzi.7 They grafted antagonistic targets of the brachial plexus using either 1 or 2 roots. Among the 12 patients in whom they identified only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover. In 1 patient of the same group who also had only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover. In 1 patient of the same group who also had only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover. In 1 patient of the same group who also had only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover. In 1 patient of the same group who also had only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover. In 1 patient of the same group who also had only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover. In 1 patient of the same group who also had only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover. In 1 patient of the same group who also had only 1 graft-eligible root, satisfactory elbow flexion was obtained in 10 patients. Simultaneous elbow extension did not recover.

In a recent article, Wang et al.61 described a small series of phrenic nerve transfers to the posterior division of the lower trunk in a very young patient population (mean age...
The surgeons obtained good elbow extension in 81.5% and good finger extension in 48% of the patients, but again, no independent movement of the elbow and fingers was obtained, which highlights the limitation of this technique, probably secondary to neuroplasticity.

One interesting hypothesis concerning nerve plasticity could be tested by examining what would happen if we connected a motor fascicle of the ulnar nerve to an elbow flexor and another motor fascicle from the median nerve to an elbow extensor. To our knowledge, no reports of this technique exist in the literature, but we could theorize that simultaneous innervation of 2 antagonists (elbow flexors and extensors) using 2 agonist muscles (finger and wrist flexors) would not provide good results for either antagonistic function because of limitations in brain plasticity.

In contrast to the poor results obtained after simultaneous reinnervation of 2 antagonistic muscles by the same agonist, it seems that a single agonist muscle reinnervated by an antagonist nerve is bound to obtain a better result, at least in the upper limb. For instance, transfer of the medial pectoral nerve (a shoulder adductor) to the axillary nerve (a shoulder abductor) is recognized as a successful technique.\(^{48,51,52}\) Similarly, Tung and Mackinnon,\(^{41,60}\) among others, successfully used distal nerve transfers for reinnervation of antagonistic functions. They selected nerve branches of the median nerve to reinnervate injured an-

tagonistic distal radial nerve branches and likewise used radial nerve branches to innervate antagonist median nerve–dependent muscles. These authors emphasized the importance of early rehabilitation for reaching a good outcome and the fact that they needed, on some occasions, to combine these procedures with a tendon transfer to obtain better functional results.

In contrast, in an analysis of the results of agonist muscle reinnervation after antagonist nerve transfer in the lower limbs (i.e., tibial branch–deep peroneal nerve transfer), the results of both experimental\(^{52}\) and clinical\(^{19}\) studies of functional foot-drop recovery were poor. We could theorize that a difference in neuroplasticity between the upper and lower limbs, induced by differences in cortical representations or subcortical/spinal circuit connections, exists. Nevertheless, more studies in this field have to be done before drawing final conclusions.

**Role of Rehabilitation**

Several published reports effectively support what has been believed for a long time: that rehabilitation after the surgical repair of BPI is very important in determining the final outcome.\(^{55,56}\)
Neuroplasticity is an influential factor in nerve transfers

FIG. 11. Results of nerve surgery in patients with both a brain injury and BPI could be worse than those in patients with only isolated BPI, which might be a result of extensive damage to the white matter subcortical networks that are involved in brain plasticity. However, this hypothesis has not been confirmed empirically. Artist: Martin Montalbetti. Copyright Mariano Socolovsky. Published with permission.

Here again an understanding of neuroplasticity influences therapy for BPI, in this case the specific forms of rehabilitation used. Therapies such as sensory reeducation, constraint-induced movement therapy, and exercise⁵⁰ target postoperative rehabilitation using this knowledge.

Sensory recovery may not only be important in restoring protective tactile sensation, it may also play a role in the modulation of neuroplasticity during motor learning. It has been hypothesized, for example, that sensory input might impede aberrant plasticity and ultimately enhance the functional motor result.⁵

Anesthetizing the forearm also was shown to yield better motor and sensory results in denervated hands.⁵⁰ It is interesting to note that a hypothesis that might explain this result could be called “controlled plasticity,” meaning that anesthetizing the adjacent cortex might impede any invasion of the really deafferentated cortex by nondeafferentated cortex, as normally occurs during brain plasticity.

Therefore, as stated by Anastakis et al.,² the keys to successful rehabilitation after a nerve transfer include 1) preoperative training that details the movements required to activate the nerve transfers, 2) repetition to reinforce plasticity, especially during the early stages of motor relearning, and 3) a minimum-length training program of 2 years, with strengthening exercises starting after initial motor movement is observed.

It has been demonstrated that exercise and electrical stimulation both promote peripheral nerve regeneration,⁵⁵ and an explanation for this finding might be that both of them enhance neuroplasticity.

Conclusions

Neuroplasticity is increasingly being recognized as one of the factors that determines the success or failure of certain nerve-transfer procedures, contributing to the effects of long-recognized influential factors such as the duration of time between the initial trauma and reparative surgery and the extent of the primary damage. Investigators who intend to develop new transfers in nerve surgery should keep in mind the principles of neuroplasticity, because the capacity of the CNS to reorganize is limited. Above all, surgical strategies and postoperative rehabilitation programs should be guided by modern concepts in neuroplasticity, because we all strive to obtain better results for our patients.

References

15. Feng JT, Liu HQ, Hua XY, Gu YD, Xu JG, Xu WD: Brain...


54. Siqueira MG, Socolovsky M, Heise CO, Martins RS, Di Masi
Neuroplasticity is an influential factor in nerve transfers. Neurosurgery 71:1156–1161, 2012


Disclosures
The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Socolovsky, Lopez, Flores. Acquisition of data: Socolovsky, Malessy, Lopez, Guedes. Analysis and interpretation of data: all authors. Drafting the article: Socolovsky, Malessy, Guedes, Flores. Critically revising the article: Malessy, Guedes, Flores. Reviewed submitted version of manuscript: Socolovsky, Malessy, Lopez, Flores. Approved the final version of the manuscript on behalf of all authors: Socolovsky.

Correspondence
Mariano Socolovsky, La Pampa 1175 Torre 2 5A, Buenos Aires 1428, Argentina. email: marianosocolovsky@gmail.com.