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RICHARD P. BUNGE MEMORIAL LECTURE

Nerve injury and repair – a challenge to the plastic brain

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Abstract Repair and reconstruction of major nerve trunks in the upper extremity is a very challenging surgical problem. Today, there is no surgical repair technique that can assure recovery of tactile discrimination in the hand of an adult patient following nerve repair. In contrast, young individuals usually attain a complete recovery of functional sensibility. The outcome from nerve repair depends mainly on central nervous system factors including functional cortical reorganizational processes caused by misdirection in axonal outgrowth. Deafferentation due to local anesthetic block, amputation or nerve transection in the upper extremity leads to very rapid cortical synaptic remodeling, resulting in a distorted cortical hand representation as well as in enlarged and overlapping cortical receptive fields. Sensory relearning programs are aimed at refinement of these receptive fields to normalize the distorted hand map and improve processing at a high-order cortical level in the context of the 'new language spoken by the hand'. As peripheral nerve repair techniques cannot be further refined, there is a need for new and improved strategies for sensory relearning following nerve repair. We propose the utilization of multimodal capacity of the brain, using another sense (hearing) to substitute for lost hand sensation and to provide an alternate sensory input from the hand early after transection. The purpose was to modulate cortical reorganizations due to deafferentation to preserve cortical hand representation. Preliminary results from a prospective clinical randomized study indicate that the use of a Sensor Glove System, which stereophonically transposes the friction sound elicited by active touch, results in improved recovery of tactile discrimination in the nerve-injured hand. Future strategies for treatment of nerve injuries should promote cellular methods to minimize post-traumatic nerve cell death and to improve axonal outgrowth rate and orientation, but high on the agenda are new strategies for refined sensory relearning following nerve repair.

Key words: cortical plasticity, nerve regeneration, nerve repair, receptive fields, sensory re-education

Clinical repair and reconstruction of injured peripheral nerves is the most challenging reconstructive surgical problem. Although the primary interest among neuroscientists focuses on central nervous system lesions, it is important to realize that injuries to the peripheral nervous system – especially nerve injuries in the hand and upper extremity – may result in considerable disability and decreased life quality because of permanently impaired hand function and lifelong pain problems. The peripheral and central nervous systems are functionally integrated with regard to consequences of a nerve injury: a peripheral nerve injury always results in a profound and long-lasting cortical reorganization *(Wall et al., 1986; Jenkins et al., 1990; Merzenich and Jenkins, 1993; Lundborg, 2000b)*.

Sensory inflow and information transfer is based on a complex pattern of slowly and rapidly adapting mechanoreceptors residing in the subepidermal, dermal,

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and subcutaneous layers of the skin, responding to pressure, vibration, and stretching *(Johansson and Vallbo, 1983; Johansson and Westling, 1984; Vallbo and Johansson, 1984; Edin and Johansson, 1995; Johansson, 2000)*. Sensory perception is the central nervous system part of the sensory experience and is based on complex processing events in the sensory networks of the brain. Nerve injuries in the hand and upper extremity are especially troublesome. Good hand function is essential for performing activities of daily life, for acting in professional life, and also for exploration of the surrounding world through the sense of touch. The hand can be regarded as an extension of the brain to the environment – it has been called 'the outer brain' by the philosopher Descartes. The sensory function of the non-injured human hand is extremely well developed and essential for hand function; protective sensibility is necessary to avoid injuries to the hand *(Brand and Yancey, 1993)*, and stereognosis, the functional sensibility of the hand, also called tactile gnosis, makes possible recognition and identification for textures and shapes *(Rosén, 2000)*. The tactile input is a code to describe the character of the environment *(Katz, 1989)*. The richness in this specific tactile information from the hand, in combination with dynamic processing capacity of the brain, has made the human hand a delicate instrument with an enormous capacity to perceive, to execute, and to express, simultaneously, in the explorative act of touch *(Gibson, 1962)*. Thus, the nervous functions of the hand are fundamental for each individual's well being. The sense of touch is important for interaction and communication between individuals. The pleasant feeling which is generated by the touch of hands has recently been linked to a special system of small-sized nerve fibers producing a faint sensation of pleasant touch. fMRI analysis during stimulation of such C tactile afferents in hairy skin has been shown to activate the insular region of the brain without activating somatosensory areas S1 and S2 *(Olausson et al., 2002)*. These C tactile afferents were identified as a system for limbic touch that may underlie emotional, hormonal, and affiliative responses to caress, like skin-to-skin contact between individuals.

The extremely well-developed sensory functions of the hand make it a sense organ, and the capacity to perform complex precision movements makes it a tool of the brain. In this perspective, a peripheral nerve injury is a catastrophe which can instantly ruin these functions. For everybody involved in the treatment of hand and upper extremity injuries, it is frustrating to experience the severe consequences of injuries to major nerve trunks and to consider how limited our possibilities are to achieve good results from surgery. Today, there is no surgical repair technique which can ensure the recovery of normal sensory functions in the hand of an adult patient following repair *(Lundborg, 1988; 2000a)*. We have reached a plateau where surgical repair techniques cannot be refined any more. Thus, there are reasons to ask whether new strategies are needed, and especially if the role of the brain may be a key factor for improving functional recovery after nerve repair *(Lundborg, 2002)*.

The aim of this lecture was to discuss the complexity of peripheral nerve injuries, with special reference to the role of the central nervous system for recovery of sensory and motor functions after nerve repair. The purpose was also to delineate some visions for the future regarding the possibilities to achieve improved results from repair of peripheral nerves, especially in the hand and upper extremity. These goals are very much in the tradition and honor of Prof. Richard P. Bunge.

The complexity of peripheral nerve injuries

Despite an enormous amount of new experimental data based on evolving neuroscientific concepts during the last three decades, peripheral nerve injuries still belong to the most challenging and difficult surgical reconstructive problems. Clinically, nerve injuries are treated in the same way as 25 years ago *(Lundborg, 2000a)*. Gradually, it has been realized that treatment of nerve injuries is not a mechanical problem but an extremely complex biological problem. In the laboratory environment, interest has shifted from primarily focusing on surgical repair techniques to basic biological mechanisms regulating and influencing key factors such as post-traumatic neuronal death *(Himes and Tessler, 1989; Aldskogius et al., 1992; Liss et al., 1994; Liss et al., 1996; Lekan et al., 1997; Vestergaard et al., 1997; Ljungberg et al., 1999; McKay Hart et al., 2002; Ma et al., 2003)*, as well as influence by the molecular composition in the local microenvironment and neurotrophic factors for growth cone mobility and axonal outgrowth and orientation *(Fu and Gordon, 1997; Olson, 1997; Frostick and Kemp, 1998; Terzis et al., 1998; Yin et al., 1998; Terenghi, 1999; Lundborg, 2000a; Nakai and Kamiguchi, 2002; Bontioti et al., 2003)*. Various types of conditioning treatments and extrinsic manipulations have been suggested such as the supply of growth factors *(Lundborg, 2000a; Boyd and Gordon, 2002)*, electrical stimulation *(Al-Majed et al., 2000a; 2000b; Brushart et al., 2002)*, electromagnetic fields *(Sisken et al., 1989; Greenebaum et al., 1996; Longo et al., 1999)* and treatment with hyperbaric oxygen *(Bajrovic et al., 2002; Haapaniemi et al., 2002)*. Advanced bioengineering techniques have been applied to create bioartificial nerve grafts based on combination of biological or non-biological scaffolds

in combination with cells and/or factors *(Lundborg, 2000a; 2003)*. Unfortunately, none of these techniques has so far reached the status of an accepted principle for clinical treatment.

However, recovery of sensory and motor functions in a hand after nerve repair is the result not only of functional, biochemical, and cellular events in the peripheral nerve and target organs, but also in dorsal root ganglia and spinal cord as well as at cortical and subcortical levels. Although early repair has been proven to reduce the death of sensory and motor neurons *(Ma et al., 2003)*, there is so far no surgical technique which can address and control the growth of individual axons – the surgeons' efforts are limited to approximation of the sheaths of the nerve *(Lundborg, 1988; 2000a)*. Regardless of the microsurgery used, we cannot avoid axonal misdirection at the repair site. The axonal misdirection which occurs at the repair site was demonstrated in the beginning of this century by Ramon Y Cajal *(1928)*, and the resulting errors in reinnervation of target tissues have recently been verified and demonstrated by use of techniques allowing direct observation of muscle reinnervation using yellow spectral variant (YFP)-labeled motor axons in transgenic mice *(Nguyen et al., 2002)*. Axonal misdirection is the basis for functional changes occurring in the central nervous system, i.e., innervation of incorrect peripheral targets is followed by a functional synaptic reorganization of the somatosensory cortex as well as motor cortex, a re-mapping of the cortical representation of the hand *(Wall et al., 1986; Merzenich and Jenkins, 1993; Garraghty et al., 1994; Silva et al., 1996; Lundborg, 1997; 2000b)*. However, functional reorganizational changes occur also at several subcortical levels. Normally, touch and other inputs from the skin become sensory perceptions via processing that begins in peripheral sensory axons and subsequently involves complex synaptic integration and transmission in spinal (dorsal horn), brain stem (cuneate and gracile nuclei), and thalamus (ventro-posterior lateral and median nuclei) *(Wall et al., 2002)*, and functional reorganizational changes following a nerve lesion may occur at all these levels. It has been suggested by Wall and colleagues *(Wall et al., 2002)* that the cortical changes are but one reflection of a global mechanism that begins moments after injury and operates at multiple subcortical and cortical levels of the somatosensory core.

From a surgical perspective, the cortical functional reorganization that follows nerve injury and repair is a key problem and one important explanatory factor for the inferior recovery of motor and sensory functions of the hand following repair of major nerve trunks in the upper extremity.

Peripheral nerve injuries – a challenge to the brain

There are several reasons to assume that the functional changes that occur in the central nervous system after nerve repair are key factors in the functional outcome and that such central nervous system factors are at least as important as peripheral factors.

1. The surgical repair technique per se plays a minor role for the functional outcome. As long as the nerve repair is carried out with care and reasonable technical skill, there is no evidence that a nerve repair performed by epineurial suture technique (placing stitches in epineurium only) results in better functional outcome as compared with group fascicular repair where the nerve subcomponents are teased apart by microsurgical techniques and individually approximated *(Lundborg, 2000a)*. In fact, the surgeon does not need to approximate the nerve ends at all if the remaining gap between the proximal and distal segments is limited and there is no interposition of adjacent tissues. In a prospective randomized clinical study on patients suffering from median or ulnar nerve lesions at wrist level, the nerve trunks were repaired either by conventional microsurgical technique or by a tubular technique, leaving intentionally a 3–5 mm of space between the nerve ends inside silicone tubes. At follow up 5 years after repair, there was no difference between the two groups regarding the recovery of sensory and motor functions in the hand *(Lundborg et al., 2003)*.

2. Restitution of functional sensibility in adults correlates with specific central nervous system cognitive capacities. In adult patients with repaired median or ulnar nerves, central nervous system factors, such as verbal learning capacity and visuo-spatial cognitive capacity, are factors helping to explain variations in the recovery of functional sensibility *(Rosén et al., 1994)*.

3. The functional outcome after nerve repair is better in children than in adults. It has long been known that the outcome from peripheral nerve repair is superior in children as compared with adults *(Önne, 1962; Almquist et al., 1983; Birch and Raji, 1991; Polatkan et al., 1998)*. We have recently shown in nerve-injured patients of various ages that nerve repair resulted in excellent recovery of tactile gnosis up to the age of 10, followed by a rapid decline to much worse results at the age of 21–25 *(Lundborg and Rosén, 2001)*. The 'time-window' in the curve for achieving maximal skill correlates strikingly well with a corresponding curve illustrating the capacity of learning to speak a second language (acquisition of the American language among Asian immigrants) (Fig. 1). The observation indicates that the recovery of sensibility is based on a learning process analogous to learning a new language – a central nervous system function.

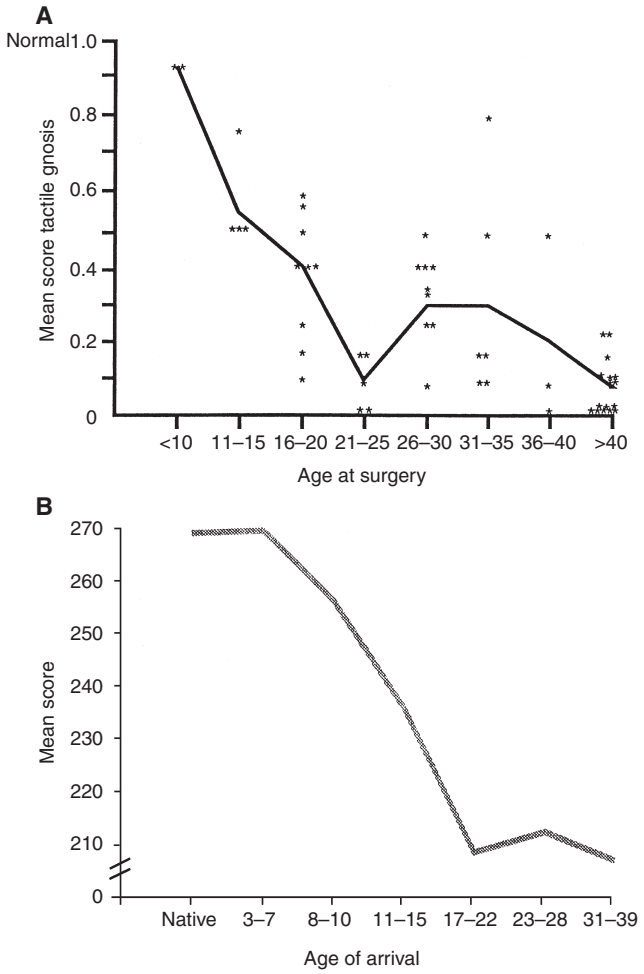

Figure1. (A) Mean recovery of tactile gnosis in 54 patients at least 2 years after injury and repair of major nerves of the forearm. (B) Telltale curve, indicating how the scores of immigrants on a grammar test decline with the age at which they started to learn to speak the English language. Both curves are strikingly alike, indicating the importance of the relearning process in both situations. From Lundborg and Rosén *(2001)*, reproduced with permission. Data in (B) is based on results published by Johnson and Newport *(1991)*.

4. A peripheral nerve injury is followed by profound and long-standing cortical reorganizational changes. Nerve injury and repair is followed by significant functional reorganizational changes in the brain cortex as well as in several subcortical structures *(Merzenich et al., 1983b; Wall et al., 1983; 1986; 2002; Garraghty et al., 1994; Silva et al., 1996; Lundborg, 2000b)*. These changes may occur within minutes after the injury and are apparent a long time after injury *(Merzenich et al., 1983a; Wall et al., 2002)*. An extended discussion of this phenomenon follows below.

The cortical hand map

The physiological basis for the sense of touch is located in the fingertips, but the true perception and interpretation is based on cortical processing of the afferent signals. These signals, elicited by tactile stimulation of the hand, are transferred to the somatosensory cortical area via relay stations in the dorsal column of the spinal cord and thalamus *(Wall et al., 2002)*. Although the cortical processing during tactile and shape perception is complex and not fully understood *(Bodegård et al., 2000; 2001)*, tactile stimuli from the hand, according to classic concepts, are processed in area 3b in the somatosensory cortex. In the classical cortical homunculus representation, the hand representation area, like the adjacent face representation, occupies a very large cortical area *(Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950),* a factor reflecting the enormous nerve cell resources that are required to serve the fine sensory motor functions of the hand (Fig. 2) *(Kaas, 1983; 1997)*. Modern brain imaging techniques like PET, MEG, and fMRI have created new and improved possibilities to map the projection of sites of the hand and fingers, data which confirm and verify what is known from several previous studies using direct cortical recordings in primates *(Merzenich et al., 1978; 1983b; Merzenich and Jenkins, 1993)*. Also, at subcortical levels (dorsal horn of spinal cord, brain stem, and thalamus), individual neurons have a receptive field on the body which, when stimulated, triggers the activation of that neuron *(Wall et al., 2002)*. At each level, all neurons with receptive fields on the same part of the body (e.g., a particular finger, the arm, etc.) group together to form a map of that body part *(Wall et al., 2002)*.

Sensory messages from the hand are processed mainly in the contralateral hemisphere but also, to a varying extent, in the ipsilateral hemisphere *(Hansson and Brismar, 1999; Bodegård et al., 2000; Lundborg, 2002)*. Also, motor functions of the hand are based primarily on activity in the contralateral hemisphere, but fMRI investigations have shown a different emphasis regarding laterality in the patterns of a cortical activity during power vs. precision grip; with more delicate hand movements more parts of the brain are engaged, including the ipsilateral side *(Ehrsson et al., 2000; 2001)*. It has recently been shown that electric microstimulation of the motor cortex in monkeys may result not only in activity in separate muscles or muscle groups, but also, when performed on a behaviorally relevant time schedule, may evoke coordinated complex movement patterns of the arm that involve many joints. For instance, stimulation of one site causes the hand to shape into a grip posture and move to the mouth *(Graziano et al., 2002)*.

Brain plasticity and functional cortical reorganizations

A cortical hand map can be defined where separate projectional finger areas constitute well-defined

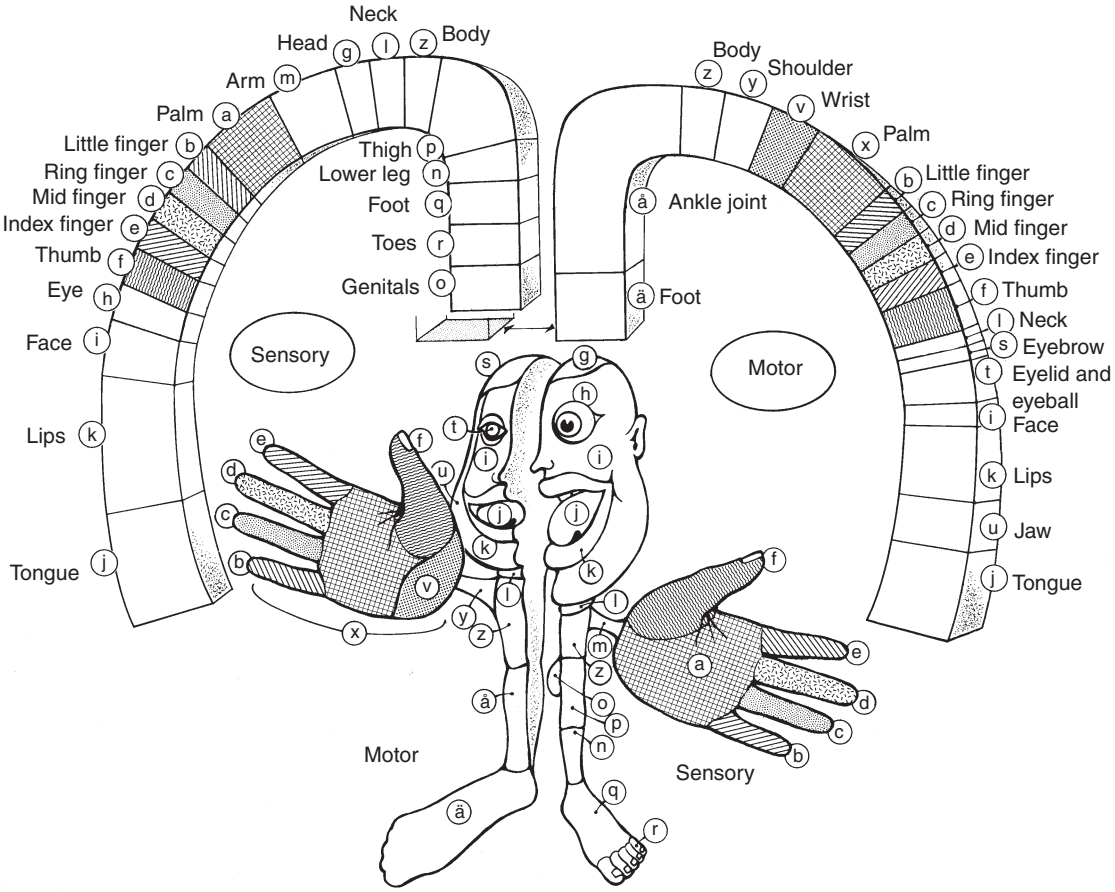

Figure 2. Cortical projections of body parts with reference to motor (anterior to central sulcus) and sensory (posterior to central sulcus) functions. Transfer sections through motor cortex (upper right) and sensory cortex (upper left) illustrate the somatotopic organization of the body parts. The homunculus figure (inspired by the original body map as proposed by *Penfield and Boldrey, 1937* and *Penfield and Rasmussen 1950*) comprised body parts in sizes proportional to their projectional areas in the brain. The projectional areas of the hand and face are very close and occupy together a substantial part of the sensory cortex (*Lundborg, 1999; 2000b;* reproduced with permission).

individual bands. It was long believed that the synaptic networks and functional organization of the brain were hard wired from birth and could not change during adult life. However, some decades ago, experiments involving direct cortical recordings from brain cortex in monkeys clearly demonstrated that the functional cortical synaptic organization can rapidly be changed and modified because of, for example, changes in peripheral input *(Merzenich et al., 1983a; Wall et al., 1986; 2002; Jenkins et al., 1990; Kaas, 1991; Lundborg, 2000b)*. The term brain plasticity indicates the brain's capacity for such synaptic reorganizations, which may occur as a response of peripheral influence immediately or extended over a longer period of time. Such changes are experience dependent and may be secondary to changes in the sensory inflow from the hand based on either modification in hand activity (increased, decreased, and non-physiological) or the result of deafferentation.

That cortical connections and cortical maps can be continuously remodeled by experience was suggested by Hebb more than 50 years ago *(Hebb, 1947; 1949)*, and the cortical representation of body parts is continuously modulated in response to activity, behavior, and skill acquisition *(Kaas, 1991; Donoghue et al., 1996; Lundborg, 2000a; Chen et al., 2002; Wall et al., 2002)*. Cortical reorganizations can be very fast or can be ongoing over longer time. Much emphasis has been put on neuronal spines, tiny protrusions from long slender dendritic extensions of nerve cells constituting the receiving parts of synapses, the connection contact that allows the signaling between neurons. There is normally a turnover of spines, although the total spine density seems to remain constant, probably reflecting some homeostatic mechanism *(Johansson, 2000; Grutzendler et al., 2002; Ottersen and Helm, 2002; Trachtenberg et al., 2002)*. However, spine density and activity can vary because of environmental influence. Experimental animals housed as adults in a stimulating environment with access to various toys and activities develop more spines per neuron than

animals housed individually in standard cages *(Johansson, 2000)*, changes that can be induced also during learning in general *(Greenough et al., 1985; Van Reempts et al., 1992; Johansson, 2000)* and by changes in sensory input *(Merzenich et al., 1983a; Kaas, 1991)*. Spines can be more or less stable. Trachtenberg et al. *(2002)* recently studied spine turnover in the barrel cortex of mice receiving sensory input from whiskers using transgenic mice in which a population of cortical pyramidal neurons expressed a green fluorescing marker protein. The fluorescence could be visualized through a thin window in the skull, using two-photon microscopy. About 20% of the spines disappeared from 1 day to the next, while about 50% of the population persisted for at least a month. Experience-dependent plasticity of cortical receptive fields was accompanied by increased synaptic turnover. For instance, when a whisker was removed, there was rapid remodelling in the corresponding cortical area so that neighboring intact whiskers became more strongly represented. This was associated with an increase in the number of transient spines – those present for a day or less – and a corresponding decrease in the number of stable spines.

Cortical reorganization secondary to changes in hand function

Cortical remodelling secondary to increased sensory input is a well-known phenomenon that has been studied in many animal models, e.g., where separate whiskers have been stimulated or removed in rats and plastic changes in the corresponding cortical representational area have been investigated *(Hand, 1982; Harris et al., 1999; Brown and Dyck, 2002)*. For instance, stimulation of one row of vibrissae results in an increased cortical representation of the trained row without interference with the representation of the adjacent row which is not stimulated during the training: the overlap between representations of neighboring rows of vibrissae became greater, and two maps co-existed within the same cortical space *(Kossut and Siuciniska, 1998)*.

Experience-induced cortical remodelling, secondary to increased tactile stimulation of separate fingers, was first demonstrated by direct cortical recordings from brain cortex in monkeys *(Jenkins et al., 1990; Merzenich and Jenkins, 1993)*. From these and later studies, it has been clearly demonstrated that representational constructs are permanently reshaped by novel experiences through dynamic competitive processes, and subjective environmental interactions play a crucial role in the maintenance of basic organizational features of somatosensory representations *(Xerri et al., 1996)*.

Thus, from a functional point of view, the hand can shape the brain – tasks requiring increased manipulatory skill result in the expansion of the cortical projectional area corresponding to the fingers involved in the task (Fig. 3). The same phenomenon is seen in blind patients using their index fingers for reading in Braille *(Pasqual-Leone and Torres, 1993)*, demonstrating a fluctuation in cortical representation dependent on reading activity pattern *(Pascual-Leone et al., 1995)*. Using MEG, Godde et al. *(2003)* showed that several hours of tactile co-activation in separated receptive fields on the right index finger resulted in a 20% improvement in spatial two-point discrimination paralleled by a rapid expansion of the cortical representational area of the finger. It has been demonstrated that the string hand of violin players, especially those who started practicing at very early ages, occupy larger projectional areas in the somatosensory as well as motor cortex of the brain *(Elbert et al., 1995)*. Long years of practice and training by professional musicians is associated with enlarged cortical representations in the somatosensory as well as in auditory domains *(Krings et al., 2000; Pantev et al., 2001a; 2001b; Pascual-Leone, 2001; Rauschecker, 2001)*.

Reorganization and expansion of activated areas may occur in the sensory as well as in the motor cortex and may be seen also in central nervous system lesions. In stroke, leaving one extremity paralyzed, it has been shown that intense training of the affected limb may result in cortical reorganizations so that cortical areas surrounding the infarct, which would not normally be involved in control of the extremity, may begin to participate in the movements *(Nudo et al., 1996; Taub et al., 2002)*. Such constrained-induced therapy may lead to recruitment of a large number of neurons in adjacent areas to participate in movements of the more affected upper extremity. Such sustained and repeated practice of functional arm movements may induce expansion not only of the contralateral cortical area that controls movement of the more affected extremity, but may include recruitment also of new ipsilateral areas *(Taub et al., 2002)*.

There is experimental evidence that diminished tactile input results in degradation of cortical representations with larger cutaneous receptive fields *(Xerri et al., 1996)*. Hands devoid of sensory experiences appear to downregulate the sensory capacity (e.g., severely contracted hands in cerebral palsy), while surgical procedures opening up the hand, making possible new tactile experience by touching objects in the surrounding, will wake up such 'sleeping sensibility' *(Dahlin et al., 1998a; 1998b)*. Hypothetically, such changes in the sensory capacity of the hand, secondary to decreased or absent tactile experiences, are reflected in the decrease and expansion of cortical

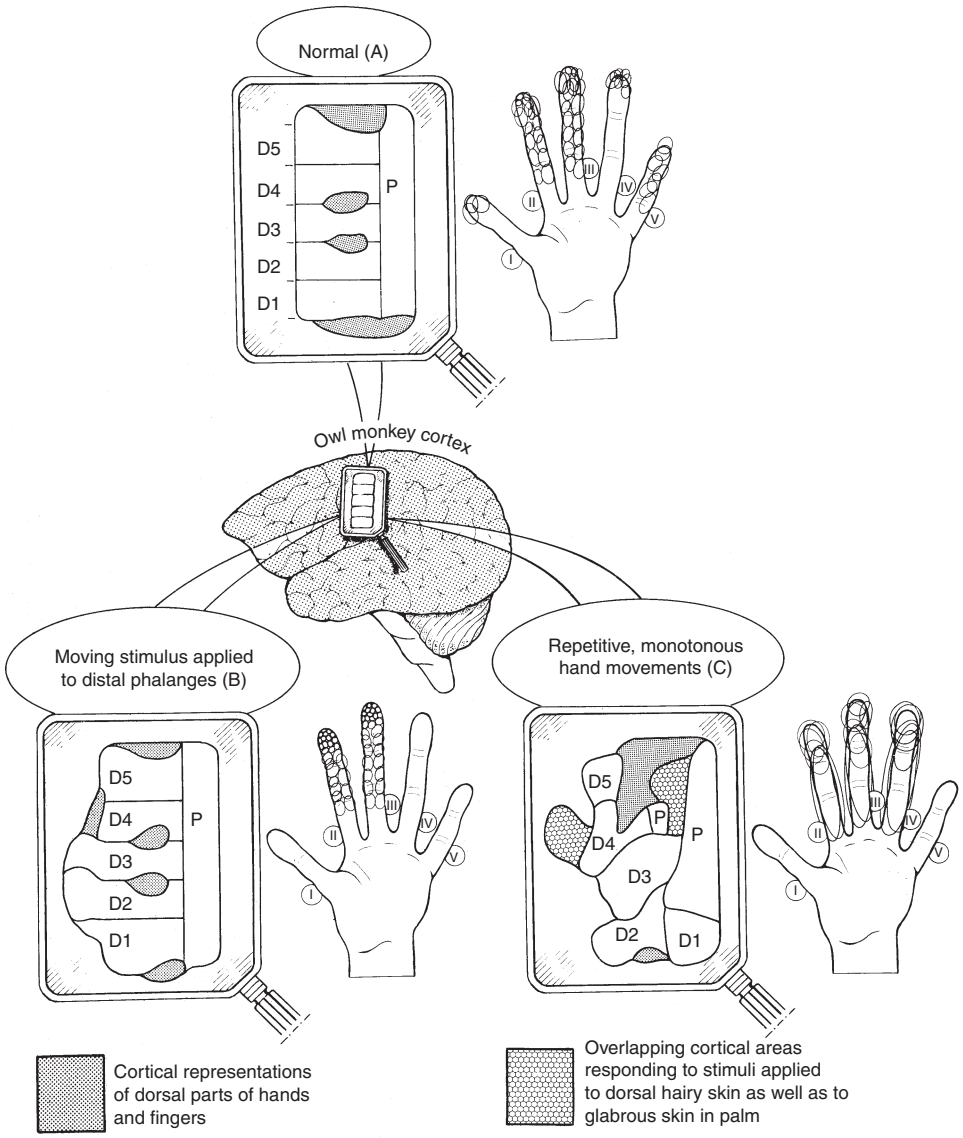

Figure 3. Activity-dependent reorganizational changes in the cortical hand map (area 3b), schematically illustrated through a magnifying glass, and examples on corresponding changes in finger receptive fields (indicated by circles and ellipsoids in hand outlines). (A) Normal cortical hand map in area 3b with sharp borderlines between individual fingers (D1–D5) and between the fingers and the palm (P). Dotted areas indicate the dorsal part of hand and fingers and are projected adjacent to digits as well as in small patches between individual digital representational areas. Receptive fields in fingers slightly overlap one another. (B) Following tactile stimulation of the second and third fingers, these fingers expand their cortical territories, and the receptive fields in the distal phalanges become small with minimal overlapping, indicating high tactile discrimination. (C) Significant changes in the cortical hand map can be induced by monotonous repetitive hand movement. The hand representation becomes degraded with de-differentiation of the cortical representations of the hand as can be seen in dystonia. The receptive fields in fingers become very large, some of them even overlapping adjacent fingers. Reproduced with permission from Lundborg *(2000b)* (based on data presented by *Merzenich et al., 1978; 1983a; 1987; Jenkins et al., 1990; Merzenich and Jenkins, 1993; Byl et al., 1996*).

hand projectional areas. The cortical hand map can be modified also by non-physiological use of the hand as seen, e.g., among musicians suffering from dystonia – an incapacity to regulate and control individual finger movements, reflected in reorganization of the hand map into a disorganized pattern (Fig. 3) *(Byl et al., 1996; Bara-Jimanez et al., 1998; Elbert et al., 1998; Candia et al., 2002)*. The reason may be non-physiological use of the hand with monotonous repetitive movements over extended time periods. A fusion of normal well-separated cortical projectional sites of individual fingers has been seen in monkeys trained to perform monotonous repetitive hand movements involving simultaneous tactile stimuli of various parts of the hand *(Wang et al., 1995)*.

Rapid cortical reorganization due to deafferentation by ischemia, anesthetic blocks, or amputation

Induction of peripheral anesthesia in fingers and hands of humans as well as non-human primates results in very fast functional changes in the cortical maps of corresponding body parts. Denervation of fingers in primates with local anesthetics results in a rapid shift of receptive fields on the anesthetic finger to adjacent intact fingers and hand locations, suggesting that acute functional cortical changes are induced as cortical maps of intact fingers expanded into the maps of denervated fingers to some degree within minutes *(Calford and Tweedale, 1991)*. Cortical sensory evoked potentials (SEPs) to stimulation of a finger change immediately following anesthetic or ischemic block of inputs from the other four fingers *(Rossini et al., 1994)*. Thus, ischemic or anesthetic block of separate fingers induces, within minutes, a cortical expansion of the adjacent fingers' representation so that their occupational areas will cover the former projection site of the anesthetic finger *(Rossini et al., 1994)*. The rapid time-course of these changes suggests that inputs from one finger normally inhibit existing inputs from adjacent fingers and that finger denervation by anesthetic block removes this inhibition *(Wall et al., 2002)*. Epidural nerve block in cats induces rapid shifts in the cortical mapping. Neurons that originally responded to stimulation of the anesthetized area become responsive to stimulation of the adjacent, unanesthetized area *(Metzler and Marks, 1979)*, a phenomenon that reverses 2–4 h after the nerve block. Thus, the cortical representations of body parts are dynamically modulated based on the pattern of afferent input *(Chen et al., 2002)*.

A very fast cortical reorganization because of unilateral deafferentation of one hand by an ischemic block has recently been described by Werhahn et al. *(2002)*. When ischemic anesthesia was experimentally induced to one hand by an inflated tourniquet around the forearm, there was an improvement in tactile spatial acuity in the contralateral hand, probably representing a behavioral compensatory gain based on a very fast synaptic reorganization *(Werhahn et al., 2002)*. One explanation may be that normally existing inhibited nervous pathways between the hemispheres are being unmasked by the ischemic block so that shifts are induced with emphasis on laterality.

Amputation of individual fingers induces a rapid cortical reorganization with expansion of adjacent cortical territories (Fig. 4) *(Merzenich et al., 1984; Merzenich and Jenkins, 1993; Weiss et al., 2000)* so that parts of primary sensory cortex that previously responded to the deafferentated body parts become responsive to inputs from neighboring body parts *(Kelahan et al., 1981; Merzenich et al., 1983a)*. In SEP studies by Weiss et al. *(2000)*, it was demonstrated that cortical dipoles of inputs from the second and fifth finger came closer together following amputation of the third and fourth fingers, thus suggesting that inputs from intact fingers reorganized to activate cortical maps of the missing finger. This reorganization occurred within 10 days after amputation.

Experiments on chronic finger and limb amputations in primates have shown that the cortical changes which occur in area 3b quickly become established and permanent. They can be seen at long (2 years) as well as short (2 weeks to 2 months) post-injury times *(Merzenich et al., 1984; Code et al., 1992; Manger et al., 1996; Wall et al., 2002)*. Long-standing amputation may result in cortical reorganization over a distance up to 14 mm in primates *(Pons et al., 1991; Manger et al., 1996)*. The changes in cortical mapping are associated with a range of functional changes also at subcortical levels *(Kaas et al., 1999; Wall et al., 2002)*.

Also within the primary motor cortex, substantial long-standing reorganizational changes occur after amputation. Qi et al. *(2000)* studied this phenomenon in young and adult primates subjected to forearm amputation, examined years after amputation. In all cases, even at 12 years after amputation, electric stimulation of those parts in motor cortex, which were formally devoted to the missing hand, now evoked movements of the stump and adjoining shoulder, indicating a substantial reorganization of motor cortex. These findings confirm previous observations that, following amputation and motor nerve lesions, the cortical area from which stimulation evoked movements from adjacent body parts enlarged, and the threshold for eliciting these movements was reduced *(Donoghue and Sanes, 1988; Sanes et al., 1990)*.

Changes in cortical maps in humans after chronic limb amputation have been studied by the use of neuromagnetic and neuroelectric source imaging, fMRI and PET. In all, these studies indicate that areas of primary somatosensory cortex that lose the hand become functionally reactivated by uninjured inputs from the face and/or arm stump *(Wall et al., 2002)*. Following traumatic amputation of an arm, there are rapid cortical reorganizational changes of the face representation as revealed in MEG studies showing a medial displacement of the face area towards the hand representation in the somatosensory cortex *(Elbert et al., 1994)*. This may give rise to a strange phenomenon as early as 24 h after an amputation – the missing hand can be mapped in the face so that touch of specific areas of the face can give rise to tactile sensations in individual fingers of the missing hand *(Ramachandran et al., 1992; Flor et al., 1995; 1998; Borsook et al., 1998)*.

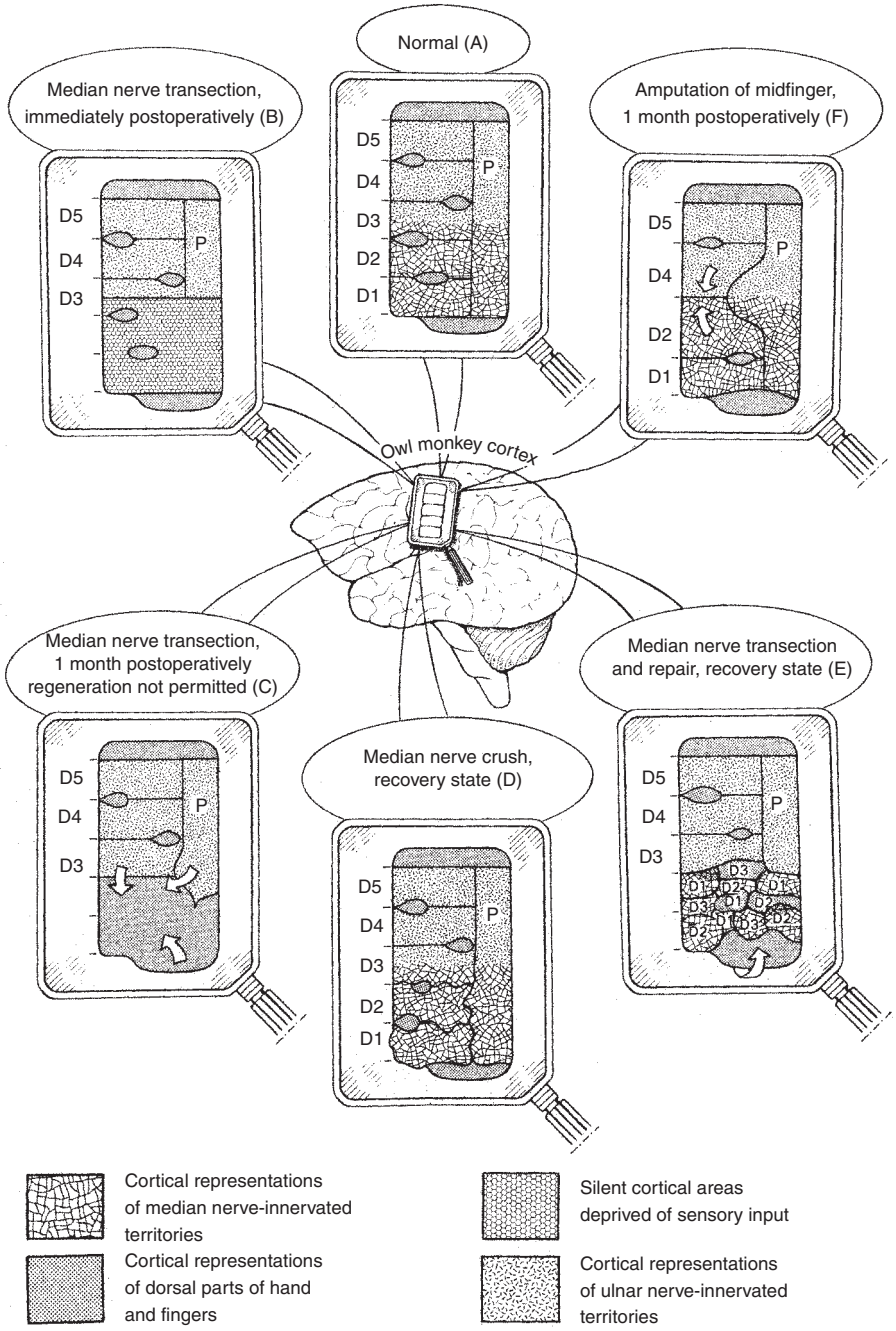

Figure 4. Cortical reorganizational changes in area 3b due to various types of de-afferentation in a primate. (A) Normal representational area of hand and fingers (D1–D5) including palm (P) and dorsal parts of fingers. (B) Immediately after a median nerve transection, the cortical area corresponding to the median nerve is acutely deprived of afferent inflow – there is a 'black hole'. (C) Within minutes to days, the cortical area, previously receiving sensory input from the median nerve, is now occupied by expanding adjacent cortical areas, i.e., corresponding to ulnar-innervated skin of the hand and dorsal radial-innervated skin. (D) Crush injury to the median nerve followed by regeneration and reinnervation of peripheral targets. The cortical representation of fingers and palm is normalized. (E) Median nerve transection followed by repair and axonal regeneration and reinnervation of peripheral targets. Owing to axonal misdirection, there is a total remodelling of the cortical median nerve representation characterized by small discontinuous patches, some of them overlapping, responding to inputs in somatotopic disorganized pattern. (F) Amputation of midfinger (D3). There is an expansion of adjacent cortical territories representing the second and fourth digits which now occupy the area previously receiving input from the midfinger (based on data published by *Merzenich et al., 1983a; 1983b; 1984; Wall et al., 1983; 1986; Allard et al., 1993; Merzenich and Jenkins, 1993*). Reproduced with permission from Lundborg *(2000b)*.

Reversal of established cortical changes has been assumed to be a key goal in the treatment of phantom pain following amputation as well as dystonia. Phantom sensations secondary to amputation are based on reorganizational phenomena at cortical and subcortical levels. Sometimes phantom pain may occur, probably because of a severe cortical reorganization combined with the deafferentation injury *(Flor et al., 1995; 1998; Knecht et al., 1995; 1998a; 1998b; Birbaumer et al., 1997)*. The extent of shift in cortical representation has been found to correlate well with the amount of phantom pain *(Flor et al., 1995; Knecht et al., 1996; Birbaumer et al., 1997)*.

The cortical reorganization secondary to amputation of the hand can be reversed if the amputated body part is reattached. By the use of fMRI techniques, it has been demonstrated that transplantation of a homologous hand to an amputee is followed by a continuous expansion of the corresponding projectional hand area in motor cortex, occurring parallel to increase in use of the transplanted hand. The hand motor projection area has been found to be regained within 6 months *(Giraux et al., 2001)*.

Reversal of the reorganizational changes has been suggested as the goal in treatment protocols for dystonia *(Byl et al., 1996; 1997; Bara-Jimanez et al., 1998; Candia et al., 1999; 2002)*.

Nerve injury

A nerve transection represents an acute deafferentation injury with immediate and long-standing influence on the corresponding representational areas in brain cortex as well as in adjacent cortical territories *(Merzenich et al., 1983b; Wall et al., 1986; 2002; Garraghty et al., 1994; Silva et al., 1996; Lundborg, 2000b; Chen et al., 2002)*.

Thus, peripheral nerve injuries cause rapid reorganization of cortical maps *(Merzenich et al., 1983a)*. The enlargement of adjacent cortical fields following injury to median and radial nerves, as described by Silva et al. *(1996)*, is followed also by shifts of receptive fields on median and radial nerve hand locations to hand locations innervated by uninjured ulnar nerve or even to the face or forearm locations.

If the axons are allowed to regenerate following the injury, the cortical remodelling scenario follows another pattern. If the injury is of a crush nature, so that axonal regeneration occurs within intact Schwann cell tubes, the original cortical hand map is re-established with time as axons reinnervate their original peripheral targets (Fig. 4); in such cases, the resulting cortical representation of the nerve will not substantially differ from the normal representation *(Wall et al., 1983)*. The re-established cortical representation harmonizes well with reinnervation of original correct peripheral targets following a crush injury *(Nguyen et al., 2002)*.

Nerve transection followed by surgical repair will result in a completely different cortical remodelling. Despite microsurgical repair techniques, there is a large extent of misdirection in axonal growth in the repair zone. Original skin areas will, to a large extent, not be reinnervated by their original axons. As revealed in primate experiments, the result is significant reorganizational changes in somatosensory cortex with a new and distorted mapping of the skin areas originally innervated by the damaged nerve (Fig. 4) *(Wall et al., 1986; Florence et al., 1994; Kaas and Florence, 1997; Jain et al., 1998)*. The former well-defined individual cortical representations of separate fingers disappear and change into dispersed discontinuous islands. Previously well-defined functional skin surfaces, e.g., the index finger, a segment of a finger, or a palmer pad, become represented across multiple small patches within the regenerated nerve cortical area. Cortical regions that recover tactile responsiveness from regenerative skin regions may contain several recording sites with abnormally located or multiple cutaneous receptive fields *(Wall et al., 1986)*. In primate experiments, nerve transection and repair results in both immediate and progressively developing changes in the cortical maps of the skin surface *(Merzenich et al., 1983b)* and at subcortical levels *(Florence et al., 1994; Wall et al., 2002)*.

We do not know whether the significant cortical reorganizational changes that have been observed in primates after nerve injury and repair also occur in humans. However, clinical experiments together with data obtained from primate experiments strongly indicate that such reorganizational changes occur and may become permanent *(Wall et al., 1986)*. At present, we are following our patients subjected to median/ulnar nerve repair with fMRI investigation at regular postoperative intervals to find out whether such changes occur and can be detected by this technique, the time course of cortical remodelling, and to what extent cortical remodelling can be modified by specific rehabilitation programs.

What are the mechanisms for cortical reorganization after nerve injury?

Various mechanisms have been proposed to explain the cortical reorganizational changes that occur following nerve injury *(Chen et al., 2002; Wall et al., 2002)*, and attempts have been made to assess how inhibitory and neuromodulatory mechanisms may contribute to reorganizational changes at cortical and subcortical levels *(Chen et al., 2002; Wall et al., 2002)*.

It seems that different mechanisms are involved to initiate very fast and more long-standing cortical reorganizations. The fast changes, occurring within minutes after deafferentation, are probably based on unmasking of previously present, but functionally inactive, synaptic connections. Such unmasking of latent excitatory synapses might help explain the rapid expansion of adjacent cortical and sensory cortical territories that follows deafferentation in humans *(Brazil-Neto et al., 1992; 1993; Sadato et al., 1995)* and nerve lesions in animals *(Merzenich et al., 1983a; Donoghue et al., 1990; Nicolelis et al., 1993)*.

Although unmasking of latent synapses can be due to several mechanisms *(Kaas, 1991; Chen et al., 2002)*, the removal of inhibition of excitatory synapses due to reduction of GABAergic inhibition is usually suggested to cause short-term plastic changes. GABAergic inhibition of synaptic function is well known, and several lines of evidence indicate that modulation of GABAergic inhibition plays a significant role in cortical plasticity *(Chen et al., 2002)*. GABA is the most important inhibitory neuronal transmitter in the brain *(Jones, 1993; Levy et al., 2002)*, and manipulation of GABA receptor function may rapidly induce shifts in cortical representations. For instance, when the GABA antagonist bicuculline is applied to the forelimb area of the motor cortex, stimulation of the adjacent vibrissae area leads to forelimb movements, suggesting that GABAergic neurons are crucial to the maintenance of cortical motor representations *(Jacobs and Donoghue, 1991; Chen et al., 2002)*. Also, several months after nerve injury, changes in the cortical distribution of GABA have been demonstrated.

Two to 5 months after median and ulnar nerve sections in primates, tests showed that cellular immunostaining for GABA was reduced in layer IV and other layers of the area 3b hand map *(Garraghty and Kaas, 1991)*, suggesting that decreased intracortical inhibition may have enhanced inputs from dorsal hairy skin. There are also studies suggesting a potential contribution of excitatory glutaminergic synapses and mechanisms involving NMDA (*N*-methyl-D-aspartate) receptors. After transection of the median nerve, there was a reduction of the expansion of the dorsal hairy skin 3b representational area when NMDA receptor antagonist (carboxypiperazine propyl phosphonic acid) was administered systemically during the first month after injury, an effect that was not present when these antagonists were given after this time *(Garraghty and Muja, 1996; Myers et al., 2000)*. Long-term potentiation of synapses requires NMDA receptor activation *(Hess and Donoghue, 1994)*. Sprouting with alterations in synapse shapes, number, size, and type may also be involved *(Kaas, 1991)*.

Sensory relearning

As a clinical routine, specific programs for sensory re-education are used in adult patients for regaining tactile gnosis *(Wynn-Parry and Salter, 1976; Dellon, 1981; 1997; Callahan, 1990; 1995; Imai et al., 1991; Rosén et al., 2003)*. According to this principle, the brain is reprogrammed in a relearning process where items of increasing difficulty are touched and explored with the eyes opened or closed. In this way, an alternate sense (vision) trains and improves the deficient sense (sensation).

However, the sensory re-education programs that we use today were designed in the 1960s and 1970s and have not changed much since then *(Rosén et al., 2003)*. Sensory re-education is based on vision guiding touch, and other cortical functions such as attention and memory are focused on several daily short practice sessions over several weeks or months *(Dellon, 1981; Wynn-Parry, 1981)*. The focus is on the plasticity of the central nervous system. Active and conscious use of the hand in daily activities combined with high motivation by the patients are factors that have been identified to be of utmost importance for the return of functional sensibility *(Callahan, 1995)*. The remodelling of cortical representation is to a great extent a function of the behavioral state as well as the strength of reward and punishment in behavioral training *(Merzenich and Jenkins, 1993)*. In animal experiments, the cortical remodelling does not occur when animals are stimulated on routine stimulus schedules, with the stimulation unattended. Non-associated meaningless inputs can drive negative representational changes, while training with the use of positive reinforcing stimuli have positive influence. By analogy, clinical sensory re-education should be carried out in a positive environment. A situation where the patient is continuously well rewarded for correct performance trials will generate the most rapid representational changes *(Merzenich and Jenkins, 1993)*.

Artificial sensibility substituting for real sensibility

The multimodal approach

It is well known that intact senses are sharpened when one sense is weakened – a well-known phenomenon among blind and deaf people *(Marks, 1983)*. According to recent concepts, the brain has a metamodal organization so that sensory deprivation in one modality may have striking effects on the development of the remaining modalities *(Bavelier and Neville, 2002)*. Plastic changes across brain systems and related behaviors vary as a function of the timing and nature of changes in experience. Multimodal brain areas show

enhanced processing of input to the remaining modalities in animals deprived of one sense and in blind and deaf humans *(Bavelier and Neville, 2002)*. PET investigations have shown that the primary visual cortex is activated when congenital and early-onset blind read Braille and carry out other tactile discrimination tasks *(Sadato et al., 1996)*. There are brain areas that are susceptible to cross-modal reorganization, the so-called polymodal association areas, which may respond to input from many various senses and may contain multisensory neurons responding to various types of sensory input *(Bavelier and Neville, 2002)*. Multisensory neurons have been found in monkeys as well as in human brains *(Gelder, 2000)*. Such neurons receive more than one type of sensory signals, e.g., vision, hearing, and touch, thus keeping the specialized perceptive areas in the brain simultaneously informed about what is happening. In general, brain areas should not be regarded as specific to one sense but rather to various tasks which require interaction of several senses at the same time, e.g., judgement of distance requiring simultaneous information of visual, tactile, and perhaps acoustic nature *(Macaluso et al., 2000; Pascual-Leone and Hamilton, 2001)*. Hypothetically, this principle may be valid also for achieving optimal perception of a structure, texture, or item that is being touched by the hand. In such a task, the simultaneous use of vision, hand sensation, and hearing (listening to the friction sound) at the same time may serve a common purpose.

Feeling by listening to the friction sound

In our efforts to develop systems for artificial sensibility, we have focused on the resemblings in perceptual experience between sound and touch that is bridged by the vibratory sense, representing a close connection between pressure sense and auditory sense *(Klatsky et al., 1987; Katz, 1989)*. Considering the delicate capacity of the hearing sense to discriminate between complex patterns of frequencies, it is reasonable to assume that hearing is able to take over functions normally devoted to touch *(Rosén and Lundborg, 2003)*. The concept is that individual textures, when being touched, are associated with very specific friction sounds and that this information can be used by the multimodal brain to identify structure and item – the patient listens to what the hand is touching.

In developing protocols for enhanced sensory relearning, we are currently using a model for artificial sensibility based on the use of acoustic signals from miniature microphones mounted at fingertip level of a non-sensate hand by use of a Sensor Glove *(Lundborg et al., 2003; Rosén et al., 2003)*. With this principle, the somatosensory cortex is provided with an alternate sensory input at a time after nerve injury when regenerating nerve fibers have not yet reached the targets *(Lundborg, 1999; Rosén et al., 2003)*. Early programs for sensory relearning can hereby be initiated long before any reinnervation of the hand can be identified, the purpose being to feed the sensory cortex with relevant information and to maintain the cortical map from the affected hand until real sensibility is present *(Rosén and Lundborg, 2003; Rosén et al., 2003)*. In clinical investigations, the principles have proved useful. In pilot cases with repaired median nerves using the Sensor Glove, recovery of tactile gnosis has been much improved as compared with control cases *(Rosén and Lundborg, 2003)*, and in a prospective randomized clinical study on patients subjected to median nerve repair at several Swedish Hand Surgery Centres, superior recovery of tactile gnosis was noted in the Sensor Glove group at 6 months follow up *(Lundborg and Rosén, 2003)*. In hand transplantation, early use of the Sensor Glove has resulted in an earlier reestablishment of the cortical representation of the transplanted hand as compared with controls not using the glove *(Lanzetta et al., 2003)*.

Enhanced sensory relearning after nerve repair

Considering the current concept of the multimodal capacity of the brain *(Pascual-Leone and Hamilton, 2001; Bavelier and Neville, 2002)*, it seems natural to use as many senses as possible simultaneously when training one missing or imperfect sense to regain its functions. Full perception of the surrounding world normally takes all senses, and the flow of impulses from the senses influences the number of activated nerve cells *(Buonomano and Merzenich, 1998)*. It is therefore natural that additional perceptual input might strengthen the experience of touch especially at a time after nerve repair when sense of touch is weakened such as at beginning reinnervation of the hand 3–4 months after a median nerve repair *(Rosén et al., 2003)*.

According to the classic Sensory Integration Theory *(Eyres, 1972)*, the central nervous system has the capacity to integrate information from more than one sensory modality. The brain gives a meaning to the combined input from several sources and then information about another without direct stimulation. For instance, an orange can be identified simply by its scent after integration of the sight, touch, taste, and smell of an orange from numerous previous sensory experiences with oranges *(Eyres, 1972)*. Smells, memories, and emotions are closely related *(Stoddart, 1990)*. In sensory relearning, it seems rational and natural to train the sense of touch while simultaneously utilizing smell, taste, hearing, and vision. For patients with weakened sensory perception, food

components with characteristic sound, flavor, taste, and smell may be useful tools to train hand sensibility, e.g., in the act of peeling an orange in a so-called 'tactile meal' *(Rosén et al., 2003)*.

Bilateral training

Classical sensory re-education programs usually involve training of the injured hand only. However, there is a firm scientific base to assume that simultaneous bilateral tactile stimulation of the injured and non-injured hands might help influence the central substrate for sensory relearning. Normally, sensory input is processed mainly in the contralateral hemisphere but there is also, to some extent, an ipsilateral activation *(Hansson and Brismar, 1999; Bodegård et al., 2000; Ehrsson et al., 2000; Lundborg, 2002)*. In rats, the whisker region of somatosensory cortex integrates information from both contralateral and ipsilateral whisker pads *(Harris and Diamond, 2000; Shuler et al., 2001)*. In patients, there is a transfer in tactile performance from a sensory trained finger to the asymmetrically opposite one, and it has been demonstrated that practice-related improvements in sensory discrimination can generalize across skin location, hemisphere, and modality *(Nagarajan et al., 1998)*. By use of transcranial magnetic stimulation, interhemispheric asymmetries in the perception of touch stimuli have recently been demonstrated, showing right hemispheric prevalence in the perception of contralateral as well as ipsilateral stimuli *(Oliveri et al., 1999)*.

Thus, bilateral touch may activate the contralateral as well as ipsilateral hemisphere. There may therefore be good reasons to use both hands in the training process, because use of additional ipsilateral pathways from the non-injured hand may provide correct tactile information to the hemisphere which is contralateral to the injured hand, thereby facilitating the learning process.

Pharmacological intervention

In cortical lesions in animals, it has been observed that amphetamine, nor-epinephrine, and other alpha-adrenergic-stimulating drugs, when combined with physical therapy, can improve functional outcome *(Hovda and Fenney, 1984; Chrisostomo et al., 1988; Goldstein and Davies, 1990; Sutton and Feeny, 1992; Johansson and Grabowski, 1994)*, whereas alpha-antagonism has a negative effect. 'Smart drugs' acting on cortical cholinergic receptors may have a potential role in the future for enhancement of cortical reorganization after reinnervation. In animal studies, an increased level of acetylcholinesterase in the sensory cortex has been associated with increased cortical plasticity *(McKenna et al., 1989; Kilgard and Merzenich, 1998)*. According to Kilgard and Merzenich *(1998)*, the basal forebrain cholinergic system plays an important role in learning by acting at muscarinic receptors to increase cortical plasticity. Cholinergic agonists such as carbachol have been shown to enhance learning *(Patil et al., 1998)*; however, acetylcholinesterase inhibitors such as physiostigmin may be more likely candidates for practical use since positive effects on learning and memory have been demonstrated *(Mohammed, 1993)*.

What are the effects of rehabilitation strategies on brain organization?

Rehabilitation involving sensory retraining can improve perceptual function, presumably through plasticity mechanisms in the somatosensory processing network, but little is known about the effects of rehabilitation strategies on brain organization *(Florence et al., 2001)*. A key question is whether such programs can result in reversal and normalization of the disturbed cortical organization or if a goal should be perceptual improvement at higher order level at the somatosensory network. Young individuals seem to have a greater capacity for normalization of the cortical hand map as compared with the adults, and in the developing brain there are machanisms that can create normalized cortical topography after nerve repair despite disordered sensory inputs *(Florence et al., 1994; 1996)*.

Recent data *(Florence et al., 2001)* add to our understanding of the effects of sensory training on perceptual improvement. Young monkeys, subjected to severance and repair of the median nerve, received enriched sensory experience postoperatively or were kept without sensory stimulation. Using direct cortical recording techniques, it was shown that an enriched sensory environment had a substantial effect on receptive field sizes in cortical area 3b with smaller and better localized fields likely to provide better resolution based on a refined representational grain of the sensory maps. Besides very fine receptive fields, there were also less-disrupted cortical maps in the sensory-enriched animals as compared with sensory-restricted animals. Thus, it is reasonable to assume that the effects of sensory relearning programs are three-folded: (1) refine cortical receptive fields with a higher sensory resolution in finger; (2) improve tendency towards reversal and normalization of the distorted hand map; and (3) improve processing in the sensory network at a higher order cortical level, facilitating interpretation of the distorted hand map.

In humans, there seems to be some capacity for normalization of cortical motor representation, at least after nerve transfer. For instance, in brachial plexus patients where intercostal nerves were transferred and anastomosed to the musculocutaneous nerve to restore biceps muscle function, the biceps muscle was

initially controlled by the intercostal area of motor cortex. However, with time, the original biceps area could access the biceps muscle via the intercostal nerve: TMS mapping studies over several years showed that the biceps representation moved laterally from the intercostal area to the arm area *(Mano et al., 1995)*. Capacity for motor plasticity is also obvious from clinical experience showing, for instance, that transfer of median nerve-innervated muscles in the forearm, normally involved in wrist flexion, can be used to replace paralyzed radial nerve-innervated muscles normally involved in the extension of wrist and fingers. The result is a shift in action of the transferred muscles, now acting as wrist/finger extensors instead of wrist flexors.

Concluding remarks

The time is past when improved surgical techniques can be expected to improve the outcome from peripheral nerve repair. As a baseline, we would like to see clinically applicable cellular strategies used to prevent or minimize post-traumatic neuronal cell death and to optimize axonal outgrowth rate and orientation. However, high on the agenda is also increased understanding of the post-traumatic cortical remodelling processes, together with refined strategies for enhanced sensory relearning to improve the outcome from nerve repair.

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