BRAIN PLASTICITY AND HAND SURGERY: AN OVERVIEW

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The hand is an extension of the brain, and the hand is projected and represented in large areas of the motor and sensory cortex. The brain is a complicated neural network which continuously remodels itself as a result of changes in sensory input. Such synaptic reorganizational changes may be activity-dependent, based on alterations in hand activity and tactile experience, or a result of deafferentiation such as nerve injury or amputation. Inferior recovery of functional sensibility following nerve repair, as well as phantom experiences in virtual, amputated limbs are phenomena reflecting profound cortical reorganizational changes. Surgical procedures on the hand are always accompanied by synaptic reorganizational changes in the brain cortex, and the outcome from many hand surgical procedures is to a large extent dependent on brain plasticity.


The human hand has often been described as an “extension of the brain”. There are several reasons for this concept. The hand is a symbol for identity, a mirror of the mind and a tool of the soul in the way our personality and psyche is expressed in gestures and movements in the body language (Lundborg, 1997). The delicate sensibility of the hand makes it a sense organ, the sense of touch being essential for exploration of the surrounding world (Katz, 1989; Klatsky et al., 1987; Manske, 1999; Vermeij, 1999). The sensibility of the hand is extremely well developed, and in active touch our fingertips can be used to identify delicate structures, forms and textures without using sight.

Sensory perception is a central nervous experience and the hand and the brain are functionally intimately linked together. The existence of cortical and subcortical topographic maps of the body surface has been well documented in primates as well as humans (Kaas, 1983). In the somatosensory cortex each body part is projected in its own representation within the postcentral gyrus of the parietal lobe (Fig 1). Body parts with specially well developed sensibility occupy larger cortical territories than those with less developed sensibility. The hand and the lips together occupy a very substantial part of the somatosensory brain cortex.

Tactile stimuli from individual fingers result in action potentials which pass through the dorsal root ganglia, up the dorsal column of the spinal cord and through intermediate relay stations (cuneate nucleus in the brain stem and ventroposterior nucleus in thalamus) on their way to the contralateral cerebral cortex. Within each nucleus there is a precise somatotopic map corresponding to locations of the original stimuli, and at all levels plastic synaptic reorganizations may take place (Florence et al., 1997; Kaas, 1991).

The hand and finger representation, located in Brodmann’s area 3B in the somatosensory cortex, have been meticulously outlined in primates by direct recording techniques from the cortical surface by Merzenich and co-workers and others (Kaas, 1997; Merzenich and Jenkins, 1993; Merzenich et al., 1978; 1987). For defining a “map” of the hand the skin surfaces effective for exciting neurons have been determined for cortical neurons within a given cortical area by carefully exploring the skin with fine mechanical probes at the same time as recordings are made from the cortical surface. The cortical receptive field defined at each sample site is the skin surface that, when stimulated mechanically, excites one or more cortical neuron(s) at the location. Typical cortical receptive fields are shown in Figure 2. Receptive fields recorded at nearby sampled locations normally slightly overlap on the skin. The extent of overlapping, and thereby also the acuity of fine tactile discrimination, may change in specific situations (further discussed below). Modern brain imaging techniques have shown an organization and mapping of the body surface in humans analogous to that found in monkeys, individual fingers of the hand being represented in well defined cortical band shaped areas.

The somatosensory cortex is topographically mapped not only along its surface – it also processes a number of distinct cellular layers arrayed vertically, perpendicular to the surface. Thus, we are dealing with an extremely complicated three-dimensional neuronal organization where cells in the various layers of the vertical columns respond to stimuli from individual parts of the hand, and where each layer sends projections on to other brain areas for further integration. In this way tactile information from the hand, generated by active touch forms the base for further processing and cortical interpretation of the sensory message, resulting in perception of characteristics of objects such as forms, shapes and textures and also qualities like density, elasticity, softness and temperature. The sublime discriminative capacity of the hand is a result of a sophisticated interaction between central nervous mechanisms and a large number of nerve endings and mechanoreceptors in the fingertips, responding to...
various types of sensory stimuli including vibration and dynamic/static touch (Edin, 1992; Edin and Johansson, 1995; Johansson et al., 1992; Johansson and Westling, 1984; Vallbo and Johansson, 1984). Until about 25 years ago it was firmly believed that the cortical mapping of body parts was firmly established in the adult brain and the widespread assumption was that sensory representations in the mature brain are fixed and incapable of functional reorganization. However, with time accumulating clinical observations have indicated that the brain is far more plastic than was previously believed, and that the potential for cortical functional re-organization is a factor of considerable practical as well as theoretical interest (Bach-y-Rita, 1967; 1981; 1990; 1994; Buonomano and Merzenich, 1998; Wynn-Parry and Salter, 1976). Merzenich and co-workers, using sophisticated techniques for direct recording from the brain cortex of primates (Merzenich et al., 1978; 1983; 1984; 1987), presented neurophysiological evidence of a capacity for reorganization in the somatosensory cortex of adult primates as a result of restricted deafferentation, for instance transection of the median nerve or amputation. Later studies have clearly demonstrated that such “plasticity” of the brain, involving extensive functional reorganizations, can in fact occur also as a result of changed sensory experience and performance of the hand, local anesthesia, as well as various surgical procedures (such as separation of sydactylies and island flap transfers). As a result of such events a functional synaptic reorganization in brain cortex can start within seconds and go on for very long time.

Recent brain imaging techniques like positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) have demonstrated that similar changes may also occur in the human brain. For instance, extensive use of hands and fingers may result in enlargement of the corresponding projectional areas in the brain (Elbert et al., 1995; Pasqual-Leone and Torres, 1993). Amputation of extremities or parts of extremities may lead to strange perceptual abnormalities such as phantom experiences and disturbed body image (Flor et al., 1995; Knecht et al., 1995; Ramachandran et al., 1992). Nerve transection and repair leads to a very significant functional reorganization in the corresponding cortical areas as a result of misdirection of outgrowing axons and aberrant innervation of peripheral skin areas. These developing concepts have presented new explanations for the variable and often disappointing results of peripheral nerve surgery, as well as the differences in outcome from nerve repair between young and adult individuals. Taken together, evolving concepts during the last two decades have substantially increased our understanding of the impact that surgical procedures in hand and extremities may have on the functional organization of the brain. Many of our results from surgery, whether encouraging or disappointing, can be explained by
central nervous changes rather than peripheral events. The aim of this comprehensive review is to present some relevant data of importance for surgeons dealing with such hand and extremity problems which can be expected to induce functional reorganizational processes in the brain.

WHAT IS PLASTICITY?
Plasticity in general can be defined as “the capability of being moulded”. Synaptic plasticity can be defined as the ability of synapses to change as circumstances require. They may alter function, such as increasing or decreasing their sensitivity; or they may increase or decrease in actual numbers. This phenomenon is thought to be the main source of the overall plasticity of nervous system pathways.

Plasticity in the cerebral cortex refers to a change in properties of cortical neurons (Ebner et al., 1997). Such changes can be detected in animal experiments with electrophysiological recording techniques, and in humans analogous studies can be performed with various noninvasive brain analysis techniques. The process of plastic reorganization is a system-wide phenomenon involving both cortical and subcortical representations (Kaas, 1991; Nicolelis et al., 1998).

Cortical plasticity can be induced by changes in activity levels that are conveyed from peripheral nerves and then transmitted to the cortex. Cortical synapses readily respond to changes in input activity by changing their strength or efficacy as a result of “synaptic competition”. In this way changes in “synaptic strength” may be activity-dependent and there are many examples of how cortical plasticity can be induced simply by changes in neural activity from the periphery. Increase in tactile stimuli may result in long-term potentiation (LTP) of cortical synapses while low rates of stimulation result in a response-decrease called long-term depression (LTD). Striking examples of activity-dependent cortical plasticity are, for instance, the findings from a number of studies on rats when whiskers are trimmed on one side of the face (Diamond et al., 1993; Ebner et al., 1997; Nicolelis et al., 1998). Within 1 to 3 days after trimming of all but two whiskers, cortical responses to stimuli from the intact whiskers are strengthened and those to the trimmed whiskers become less able to drive cortical cells (Diamond et al., 1993).

Much attention has been paid to the biochemical mechanisms underlying plasticity and reorganizational changes occurring in the somatosensory cortex. The main excitatory neurotransmitter in the mammalian brain is the aminoacid glutamate, and among glutamate receptors the NMDA receptors (responding to N-methyl-D-aspartate) have gained the greatest attention (Ebner et al., 1997). The synaptic strengthening is thought to involve the NMDA receptor complex since limited reorganization occurs in the somatosensory cortex if NMDA receptors are blocked during the recovery period following nerve injury (Florence et al., 1997; Garraghty and Muja, 1996; Kano et al., 1991), and it has also been demonstrated that glutamate receptor blockage at cortical synapses has consequences for cortical functional organization during development (Fox et al., 1996). Rapid activity-dependent changes may reflect inhibitory and facilitatory modifications in

Fig 2 Activity-dependent changes in cortical mapping (area 3b), schematically demonstrated through a magnifying glass, and examples on corresponding changes in finger receptive fields induced by behaviourally controlled tasks (owl monkeys). Receptive fields are indicated by circles and ellipsoids in hand outlines. (a) Normally there is a well organized cortical map of the hand and fingers in area 3b with sharp borderlines between individual fingers (D1–D5) and between the fingers and the palm (P). The hairy skin of the dorsal part of hand and fingers (dotted areas) is projected adjacent to the digits and also in small patches in between individual digital representations. Receptive fields in fingers, as indicated schematically to the right, slightly overlap one another. (b) Moving stimulus applied to distal phalanges of second and third fingers. The two stimulated fingers expand their cortical territories. The receptive fields in the distal phalanges become unusually small with minimal overlapping. (c) Monotonous repetitive hand movement results in significant changes in cortical mapping. The hand representations become markedly degraded with dedifferentiation of cortical representations of skin of the hand. The receptive fields in fingers become very large, some of them even overlapping adjacent fingers. [Based on results and drawings from Jenkins et al. (1990), Merzenich and Jenkins (1993), Merzenich et al. (1978; 1987), Byl et al. (1996).]
synaptic functions (Ebner et al., 1997). More long-standing de-afferentiations, like those produced by amputation and nerve injuries, may reflect – at least in part – formation of new connections (Florence et al., 1997; 1998). Activity-dependent alterations may occur also in the motor cortex. For instance, it has been demonstrated in monkeys that after behavioural training for tasks requiring skilled use of digits the corresponding digit representation in motor cortex expands; these changes may be progressive and reversible (Nudo et al., 1997).

CORTICAL REORGANIZATION AS A RESULT OF CHANGES IN SENSORY EXPERIENCE AND PERFORMANCE

It has been demonstrated in several experiments on primates that cortical functional reorganization changes in the cortical representational fields may occur in a use-dependent manner. Extensive active use of specific fingers as well as new sensory experiences in the hand may result in such functional reorganization in the somatosensory cortex (Fig 2). In experimental animal studies, areas 3a and 3b in primates have been mapped before and after several weeks of a period of behaviourally controlled hand use. For instance, owl monkeys were conditioned in a task that produced moving cutaneous stimulation of a limited sector of skin on the distal phalanges of one fingers; in order to obtain food the distal aspect of the distal segment of digits maintained contact with a ridged rotating stimulus disk for 10 to 15 seconds per banana pellet reward. Analysis of cortical mapping data several weeks after such a training period showed that the stimulated skin surfaces were now represented over extended cortical areas. The receptive fields of the fingers were unusually small and in fact represented the stimulated skin surface in very fine spatial grain (Jenkins et al., 1990; Merzenich and Jenkins, 1993). In these situations every small skin locus provided sensory inputs that could effectively compete with inputs from nonstimulated skin areas. As a consequence, smaller than normal receptive fields are generated as the cortical network creates an abnormally fine-graded, spatially devolved representation of the stimulated skin surface.

It can be assumed that any behaviourally important use of the hand requiring delicate sensory feedback and discrimination would have impacts on the details of corresponding cortical representations as well as the size of receptive fields in the fingers (cf. Braille reading, discussed below) and that active touch, associated with use of the hand as an “exploratory” organ in fine sensory task, may lead by cortical synaptic changes to increased skills. It is well known that practice of haptic skills in general generates substantial improvements in recognition skills, stimulus discrimination and also motor performance (Gibson, 1953). There are reasons to believe that such improvement in skill and capacity may be due to practice-induced cortical representational changes, and that synaptic plasticity associated with long-term learning processes in general can explain many such phenomena.

In other experiments adult owl monkeys were trained to use the normal hand in a frequency discrimination task. The animals were trained to detect a difference in the frequency of sequentially applied tactile stimuli presented to a constant, restricted location on the glabrous skin of a single finger by a vibrating probe. The animals were trained to identify a 20 Hz stimuli, and correct responses were rewarded with a food pellet. By decreasing the threshold for frequency discrimination over time, the animals’ ability to make even finer discrimination of frequencies was improved by the training. In these experiments the stimulus was brought down repeatedly on to a constant skin site restricted to a small part of a segment of one finger and the monkey was trained to make distinctions about the temporal patterns of applied stimulation (Recanzone et al., 1992a; 1992b; 1992c; 1992d). It was found that the frequency difference discrimination performance of the monkeys improved progressively with training. The cortical representation of the trained hands became substantially more complex in topographic details than the representations of the unstimulated hands. In well-trained monkeys a large cortical area representing the stimulated skin area, significantly greater than on the control side, emerged. However, the receptive fields representing the trained skin were significantly larger than on the control digits, the largest receptive fields being centered in the zone of representation of stimulated skin. Receptive fields also enlarged all across the zones of representation of adjacent fingers. Thus, the training resulted in a genuine progressive improvement in temporal acuity specific to the trained skin (frequency discrimination capacity), but due to the increase in size of receptive fields, spatial acuity and haptic abilities probably became worse. In clinical terms the experiments illustrate that tactile capacity can presumably be substantially degraded by certain forms of conditioning or training. The findings may presumably have relevance for the disturbance in sensibility and fine motor functions seen in patients exposed to vibration by handheld tools (Cederlund et al., 1998).

It has been shown that in humans cortical functional reorganization can also take place as a result of changes in peripheral sensory performance and experience. For instance, in young string instrument players the left (fingering) hand representation in somatosensory cortex has been found to be larger than that of the right hand (Elbert et al., 1995). On both sides the hand representations are larger than those in matched controls who never played the violin. The extent of cortical reorganization is correlated to the age at which the child initially began to play the violin. The interpretation of these data is that the cortical representation of the digits
had expanded as a function of prolonged high frequency peripheral input activity, in this case the result of daily practice. It has also been shown that in blind Braille readers, “reading” with the index finger, there is an expanded sensory and motor cortical representation of this finger relative to that of non-reading fingers and to that of matched control individuals (Pasqual-Leone and Torres, 1993). Interestingly enough it has been demonstrated that the visual cortex is very active in Braille readers who are actively reading during the imaging, but not as a result of passive stimulation of the finger by a Braille reading device (Sadato et al., 1996).

In reconstructive hand surgery a striking example of brain plasticity is how stereognosis in the hands of children suffering from cerebral palsy may be improved by surgery that is aimed at exposure of the palm to the environment. With severe flexion deformity of the wrist in spastic disease the hand is not exposed to tactile experiences and stereognosis functions are poor. Such “sleeping sensibility” can, however, be awoken following a tendon transfer which releases the wrist contracture and puts the hand in a more functional position so that the palm of the hand can be subjected to new tactile stimuli (Dahlin et al., 1998a, 1998b).

However, there may also be potential negative consequences of frequent and stereotyped use of fingers. Repetitive tasks may be implicated in dystonias (writer’s cramp) and “repetitive strain injuries” (RSI) (Byl and Melnick, 1997; Byl et al., 1996). It seems that overacting the normal mechanisms by stereotyped use of the fingers may result in significant cortical reorganization. In experimental studies primates were required to squeeze and release a pistol grip in less than three-quarters of a second in a stereotyped fashion to obtain its food reward. With time the animals’ capacity to perform this task declined and they showed remarkable difficulties in opening and closing their hands. An unusual representation of the surface of the trained hand in cortical area 3b could be demonstrated (Fig 2c). The hand representation was found to be markedly degraded in these monkeys as characterized by a dedifferentiation of the cortical representation of the skin of the hand manifested by receptive fields that were 10 to 20 times larger than normal. Many receptive fields emerged that covered the entire glabrous surface of individual digits or that extended across the surface of two or more digits. A break-down of the normally sharp delineations between the receptive fields for individual fingers was seen, and some cortical neurons responded to a touch anywhere on the front of the hand. Thus, there was a degradation of cortical representation of sensory information guiding fine motor hand movements and it was felt that these findings might help to explain dyscoordination phenomena with disturbances in fine motor function as a result of long-term stereotyped and monotonous use of the fingers. Analogous findings have been made by Bara-Jimanez et al. (1998) in dystonic patients by the use of a large number of external scalp electrodes. Similar observations have also been made in dystonic musicians by the use of MRI techniques (Elbert et al., 1998) and in patients with writer’s cramp by the use of PET technique (Tempel and Perlmutter, 1993). Specific therapeutic programs have been suggested to compensate for such central nervous organization alterations (Candia et al., 1999).

**EFFECTS OF LOCAL ANAESTHESIA**

The synaptic plasticity of the adult brain allows very rapid functional reorganizations. Cortical receptive field shifts can be detected within a few seconds after induction of peripheral sensory deafferentation such as digital amputation (Calford and Tweedale, 1988) as well as injury to digital nerves (Calford and Tweedale, 1991) and the median and radial nerves of primates (Silva et al., 1996). Local anaesthetic blocks may induce prompt shifts in neuronal receptive fields, lasting for only a few hours (Nakahama et al., 1966; Nicolelis et al., 1993; Pettit and Schwark, 1993; Rossini et al., 1994). Neurons displayed their normal receptive fields as soon as the effect of the local anaesthesia wore off. The findings suggest that the adult somatosensory cortex has the capacity for considerable rapidly reversible functional reorganizations over a very brief period of time.

**SURGICAL PROCEDURES**

**Separation of syndactyly**

Remodelling of the cortical area 3b has been observed in primates subjected to surgical fusion of two fingers: the previously sharply distinguished cortical receptive fields of the individual fingers were no longer evident following surgery and there was a “fusion” in the cortical representation of the fingers (Allard et al., 1991). With separation of fused fingers the reversed reorganization took place. Analogous observations have been made in humans. In patients born with fused fingers, presurgical maps based on magnetoencephalography have shown no separate representational cortical areas, corresponding to the fused fingers, whereas post-surgical maps have revealed that the cortex has reorganized so that the separated digits were separated in the cortical areas (Mogilner et al., 1993).

**Island flap transfer**

A well known technique to resurface the pulp of the thumb with sensate skin is to use an innervated pedicled skin island flap transposed from the ulnar part of the ring finger to the thumb (Paneva-Holevich and Holevich, 1991; Tubiana and Duparc, 1961). In primate experiments such procedures result in a functional remodelling of area 3b corresponding to the thumb receptive fields (Merzenich and Jenkins, 1993; Merzenich et al., 1993). After 3 months the cortical
invasive brain imaging techniques a strong relationship suggested that the amount of phantom pain might be sensations may be painful or not painful. It has been (Kew et al., 1994). Amputees may suffer from various is reflected also in reorganizations of cortical blood flow ordinarily inactive synapses. axon terminals, e.g. a result from disinhibition of phenomenon may be due to the rapid unmasking of organized modality-specific manner to distinct points face can be referred in a precise, topographically organized modulation of sensory pathways may occur very soon after amputation in humans: in less than 24 hours after amputation of a limb, receptive fields representing different capacities for cortical reorganization and synaptic plasticity between monkeys and humans.

AMPUTATION

It is well known that people who have lost a limb or parts of an extremity may often suffer from strange and embarrassing “phantom limb sensations” after the amputation. Such patients may experience a virtual empty space which may have quite an impact on their body image (Berlucchi and Aglioti, 1997; Ramachandran, 1998). Clinical data as well as results from brain imaging investigations provide evidence that a cortical reorganization may rapidly occur after an amputation. Touching a body part may evoke a sensation in the limb that has been amputated and the touch may be associated with phantom pain effects (Flor et al., 1995; Knecht et al., 1995; McAllister and Calder, 1995; Ramachandran et al., 1992). A well known phenomenon is that touching areas on the face or upper arm may induce tactile sensations referenced to a lost hand (Halligan et al., 1994; Ramachandran, 1993; Ramachandran et al., 1992). The phenomenon is due to a rapid cortical reorganization with expansion of adjacent cortical areas into the area previously activated by inputs from the amputated limb. Such a reorganization of sensory pathways may occur very soon after amputation in humans: in less than 24 hours after amputation of an arm, stimuli applied on the ipsilateral face can be referred in a precise, topographically organized manner to distinct points in the phantom limb (Borsook et al., 1998). Such a phenomenon may be due to the rapid unmasking of ordinarily silent inputs rather than sprouting of new axon terminals, e.g. a result from disinhibition of ordinarily inactive synapses.

Thus, amputation of a limb is followed by a significant cortical reorganization, a phenomenon which is reflected also in reorganizations of cortical blood flow (Kew et al., 1994). Amputees may suffer from various extents of phantom sensations and such phantom sensations may be painful or not painful. It has been suggested that the amount of phantom pain might be associated with the extent of cortical reorganization which takes place following the amputation. Using non-invasive brain imaging techniques a strong relationship between the amount of cortical reorganization and the magnitude of phantom limb pain experienced after arm amputation has been reported (Birbaumer et al., 1997; Flor et al., 1995; Flor et al., 1998; Knecht et al., 1995; 1998a, 1998b). It was proposed that phantom-limb pain may be related to, and may be a consequence of, plastic changes in the primary somatosensory cortex. Prevention of such plastic changes could therefore, hypothetically be a potential way to prevent occurrence of phantom limb pain, for instance by pharmacological blocking of glutamate-receptors. As stated above, blockage of such receptors may prevent or interfere with functional reorganization following nerve injury and during development. Treatment with ketamine (an NMDA-receptor antagonist) has been successfully tried for the treatment of phantom pain (Nikolajsen et al., 1996; 1997). However, the aetiology of phantom pain is probably very complex and to a large extent unknown (Katz, 1992; Melzack, 1990). It has been suggested that phantom sensations may activate a memory track (Melzack, 1990) and that the mechanism for the amputation injury may thereby play a role. Neuramagnetic source imaging has revealed minimal reorganization of the primary somatosensory cortex in congenital amputees and traumatic amputees without pain while amputees with phantom limb pain showed massive cortical reorganization (Flor et al., 1998).

Amputation of a limb is also followed by cortical reorganization in the motor cortex, although it has been shown by the use of fMRI techniques that representational areas in the motor cortex, normally driving movements of the hand, may be well preserved following amputation. Motor cortex activity was studied by Ersland et al. (1996) during real (left hand) and imaginary (right hand) finger tapping in a man who had his right arm amputated 1.5 years earlier. He was instructed alternately to move the intact left hand fingers and to imagine tapping the fingers on the amputated right hand. Activation was observed in the right motor cortex during finger tapping with the intact left hand, and a corresponding activation in the left motor cortex for imaginary movements of the fingers of the amputated right hand.

The physiology of phantom sensations can be best understood in the light of primate experiments. (Merzenich et al., 1984; Nicoléis, 1997). It has been demonstrated that phantom limbs could in fact be explained as true physiological responses. Merzenich et al. (1984) amputated the mid finger of primates and later stimulated the digits on the hand that were adjacent to the amputation stump (Fig 3). By using microelectrodes to detect activity in neurons in various cortical areas it was found that the region of the somatosensory cortex that originally responded to stimulation of the amputated finger was now triggered every time the two adjacent fingers were touched (Merzenich and Jenkins, 1993; Merzenich et al., 1984). Immediately following digital amputation, receptive fields representing
surrounding skin surfaces greatly enlarged and expanded over the cortical area that previously represented the middle finger. In the monkey experiments most or all of the area formerly representing the missing digit was occupied by new inputs from the adjacent fingers and subadjacent palm (Merzenich et al., 1984), evidence of expansion of topographic representation.

**NERVE INJURY**

Transection of a peripheral nerve represents a partial deafferentiation with immediate and long-standing influence on the representational area in brain cortex corresponding to that specific nerve (Garraghty et al., 1994; Merzenich et al., 1983; Silva et al., 1996; Wall et al., 1986). For instance, transection of a median nerve of primates immediately results in a silent “black hole” in the somatosensory brain cortex corresponding to the projectional areas of thumb, index finger, middle finger and half ring finger (Fig 3). Significant inputs restricted to the dorsum of the hand and digits were immediately “unmasked” by the median nerve transection (Merzenich et al., 1983) and gradually the adjacent ulnar territory expands to occupy a substantial area of the former median nerve territory (Silva et al., 1996). Within 1 week its cortical territory is completely occupied by expanding adjacent cortical areas representing surfaces on the dorsum of the hand as well as the glabrous skin of the radial and ulnar parts of the hand. Initially this emerging input is crude and emerging receptive fields are abnormally large and overlapping. However, with time the cortical topography is subjected to further extensive refinement and within 2 to 3 weeks the topography of representation of the new inputs in this zone is refined and shows sharp borderlines between the expanding territories from adjacent cortical areas (Merzenich and Jenkins, 1993; Wall et al., 1986).

Thus, the former median nerve cortical territory is rapidly occupied by the adjacent cortical areas following deafferentiation. After this the subsequent development is dependent on the nature of the nerve lesion. If the median nerve is not permitted to regenerate the extensive reorganization of the cortical map, as described above, persists so that the cortical area, previously receiving input from the median nerve, remains completely occupied by expanding adjacent cortical areas (Fig 3c). If we are dealing with a crush injury, followed by regeneration, the picture is totally different – since regenerating axons can follow their original Schwann cell tubes they also reach their original skin locations (Lundborg, 1988). The resulting cortical representation of the median nerve innervating skin areas after regeneration will therefore not substantially differ from the normal representation (Fig 3d) (Wall et al., 1983).

However, if the median nerve is subjected to transection and repair there will be a completely different cortical remodelling scenario. Due to randomized growth in the repair zone and misdirection in axonal growth the original skin areas will, to a large extent, not be reinnervated by their original axons. This will result
in significant reorganizational changes in the cortex, specifically restricted to those regions where input from the median nerve are normally represented (Fig 3e) (Florence et al., 1994; Jain et al., 1998; Kaas and Florence, 1997; Wall et al., 1986). In primate experiments the median nerve did not recapture all of its original territory. The former well defined band-like cortical representations of individual fingers now disappeared and changed into dispersed discontinuous islands. Any previously well defined functional skin surface, e.g. the thumb, the segment of a finger or a palmar pad, became represented across multiple small patches within the regenerated nerve cortical area. The functional features of cortical regions that recovered tactile responsiveness from reinnervated skin regions was abnormal in several respects. These regions contained several recording sites with abnormally located or multiple cutaneous receptive fields (Wall et al., 1986). Over a long period of observation the cortical representational loci of many skin sites appeared to change continuously, and often markedly, and the location of map discontinuities also shifted significantly over time. Thus, nerve transection results in both immediate and progressively developing changes in the cortical maps of a skin surface (Merzenich et al., 1983).

Plastic synaptic change occur also in the cuneate nucleus at the brain stem level (Florence et al., 1994).

The functional reorganizational changes in cortex following nerve repair correspond well to the situation in humans in whom, for example, median nerve suture in adults results in loss of fine sensory functions such as tactile gnosis/stereognosis (McAllister and Calder, 1995). The hand “speaks a new language to the brain”, and a period of sensory reeducation (Fig. 4) is required to acquire functional sensibility as described by Wynn-Parry and Salter (1976), Dellon (1981), Callahan (1990) and Imai et al. (1991). According to this principle the brain is “reprogrammed” in a re-learning process where items of increasing “difficulty” are touched and explored with the eyes open or closed. An alternative sense (vision) is used to improve the deficient sense (sensation).

Little is known about the true synaptic events taking place during sensory reeducation. The training may make the mind cope with new, more or less permanent, cortical reorganizations in the somatosensory area, thereby regaining a capability to understand shapes, forms and textures. The training might perhaps even modify and reverse the abnormal cortical map towards a more normal pattern. However, whatever the

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**Fig 4** Principles for sensory reeducation following median nerve injury and repair. (a) Diagrammatic representation of normal “mapping” of a round ball in somatosensory cortex. (b) Following nerve transection and regenerating nerve fibres, the mapping is completely changed due to axonal misdirection and subsequent functional reorganization in the sensory cortex. (c, d) In the sensory reeducation programme, visual and tactile impressions are combined to train the brain to understand the “new language spoken by the hand”. [From Lundborg (1999).]
mechanism, a growing number of studies of cortical plasticity reveal that remodelling of cortical representations is to a great extent a function of the behavioural state and a function of the strength of reward or punishment in behavioural training (Merzenich and Jenkins, 1993). Thus, cortical remodelling and change in receptive fields towards smaller sizes as a result of training based on moving stimulation do not occur when animals are stimulated on routine stimulus schedules with the stimulation unattended. It seems that non-associated “meaningless” inputs can actually drive negative representation of changes in cortical representations while training with the use of positive reinforcing stimuli has a positive influence. In such a behavioural context representational changes progress gradually over a relatively slow daily improvement schedule.

The clinical implications is that sensory reeducation should be carried out in a positive environment. Passive, unattended or occasionally attended exercises are of limited value for driving central representational changes. The more important the training exercise, the more powerful its consequences. The more feedback a subject gets, relevant to correct response performance, the faster useful representational changes can be driven. The practice setting in which the patient is continually rewarded for correct performance trials will generate the most rapid representational changes (Merzenich and Jenkins, 1993).

From the therapeutic point of view, rehabilitation following injuries in the peripheral nervous system may have some interesting analogies with injuries in the central nervous system, such as stroke. In both situations functional recovery is greatly dependent on brain plasticity and cortical functional reorganization (Johansson and Grabowski, 1994). In animal experiments it has been observed that amphetamine, nora-ldrenalin and other alpha-adrenergic stimulating drugs, when combined with physical therapy, can improve functional outcome after cortical lesions (Chrisostomo et al., 1988; Goldstein and Davies, 1990; Hovda and Fenny, 1984; Johansson and Grabowski, 1994; Sutton and Feeny, 1992) whereas alpha-antagonists may have a negative effect. Sensory reeducation following nerve lesions to facilitate and improve the necessary cortical functional reorganizations in the somatosensory cortex combined with drug therapy may perhaps be a way to improve the outcome in the future.

Various factors may help to explain the ability by adults to compensate for cortical reorganization after nerve injury. Cognitive capacity factors may play an important role for the functional outcome following nerve repair, and variations in such factors – especially verbal learning and visio-spatial logic capacity – may help to explain variables in recovery of functional sensibility following nerve repair (Rosén et al., 1994).

However, the most significant factor to explain differences in recovery of functional sensibility is the age of the patient (Rosén et al., 1994). It is well known that sensory recovery following nerve injury and repair is much better in young patients than adult patients (Almquist and Eeg-Olofsson, 1970; Almquist et al., 1983; Kallio and Vastamäki, 1993; Onne, 1962; Stromberg et al., 1961; Tajima and Imai, 1989); a fact that has usually been explained by factors like shorter regeneration distances and greater regeneration potential. A major explanation is that there is probably a higher potential for brain plasticity in children compared to adults. Such a difference has recently been demonstrated in experiments carried out on fetal monkeys. Following median nerve section and surgical repair in immature monkeys the resulting representation of the reinnervated hand in primary somatosensory cortex is quite orderly in spite of there being little or no topographic order in the regenerated median nerve (Florence et al., 1996). The findings indicate that there are mechanisms in the developing brain that can create cortical topography despite disordered sensory inputs.

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References


