REVIEW

# Brain plasticity in health and disease

**Barbro B Johansson**

*Division for Experimental Brain Research, Department of Clinical Neuroscience, Lund University, Wallenberg Neuroscience Center, Lund, Sweden*

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**Abstract. Research during the last decades has greatly increased our understanding of brain plasticity, *i.e.* how neuronal circuits can be modified by experience, learning and in response to brain lesions. Currently available neuroimaging techniques that make it possible to study the function of the human brain *in vivo* have had an important impact. Cross-modal plasticity during development is demonstrated by cortical reorganization in blind or deaf children. Early musical training has lasting effects in shaping the brain. Albeit the plasticity is largest during childhood, the adult brain retains a capacity for functional and structural reorganization that earlier has been underestimated. Resent research on Huntington's disease has revealed the possibility of environmental interaction even with dominant genes. Scientifically based training methods are now being applied in rehabilitation of patients after stroke and trauma, and in the sensory retraining techniques currently applied in the treatment of focal hand dystonia as well as in sensory re-education after nerve repair in hand surgery. There is evidence that frequent participation in challenging and stimulating activities is associated with reduced cognitive decline during aging. The current concept of brain plasticity has wide implication for areas outside neuroscience and for all human life.** (Keio J Med 53 (4): 231–246, December 2004)

**Key words: neuronal plasticity, development, dystonia, stroke, aging**

## Introduction

The unique evolution of the human brain is the basis for the development of human culture, science and technology. Our neurons are tuned in close interaction with our environment, our own activities and thoughts. Interaction between genes and environment is evident from the global variations in customs, languages, and culture. Ernesto Lugano, an Italian psychiatrist may have introduced the term plasticity in neurosciences as early as 1906.[1] However, the important studies in this field were initiated by Donald Hebb, who more than half a century ago postulated that neuronal cortical connections are strengthened and remodeled by our experience.[2] He showed that rats that were allowed to run around freely in his house were better learners and had better memory capacity than rats housed in the laboratory.[3] Many studies have shown that an activity-stimulating environment has multiple effects on the brain including increasing the number of neuronal connections.[4–9]

Dendritic spines, *i.e.* tiny protrusions on the dendrites (Fig. 1)[10] are the primary postsynaptic targets of excitatory glutaminergic synapses in the mature brain, and they have been proposed as primary sites of synaptic plasticity.[11,12] The dendritic tree is covered with a variety of excitable synaptic channels operating on different time scales and with activity-dependent sensitivity enabling a sophisticated neuronal plasticity.[13] The spine cytoskeleton consists of actin filaments, and video recordings from hippocampal neurons expressing actin tagged with fluorescent protein have shown that the shape of spines can change rapidly,[14] events that are accompanied by changes in calcium influx and decay.[15,16] With a technique enabling *in vivo* images of neurons expressing green fluorescent protein, the lifetime of superficial pyramidal spines in the mouse barrel cortex has been observed to vary greatly.[17] About 20% of spines disappeared from one day to the next, a loss that was balanced by formation of new spines. About 60% of dendritic spines persisted for at least 8 days, and of those 17% had disappeared one months after the

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Reprint requests to: Dr. Barbro B Johansson, Wallenberg Neuroscience Center, BMC A13, SE- 221 84 Lund, Sweden, telephone: +46-46-222 0621, facsimile: +46-46-222 0626, e-mail: Barbro.Johansson@neurol.lu.se

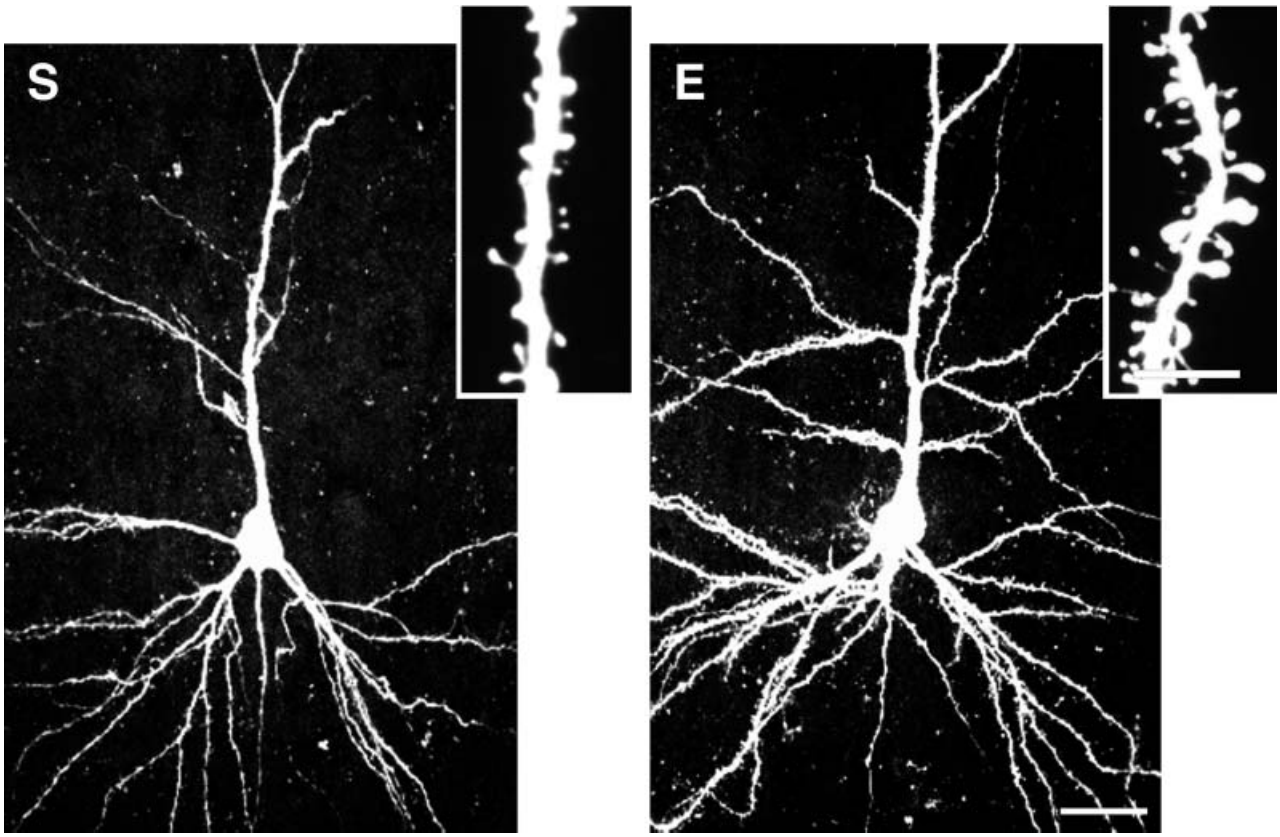


**Fig. 1** Pyramidal neurons in cortical layer III in male 4 months' old spontaneously hypertensive rats housed in standard environment (S), or housed in an enriched environment (E). Standard housing = 3 rats in each cage; enriched housing = 8 rats in larger cages with opportunities for various activities. The environmental enrichment significantly increases dendritic branching and number of dendritic spines (insertions). (Reproduce from, Johansson BB, *et al*: In: Bazan NG, *et al* eds, Maturation Phenomenon in Cerebral Ischemia IV, Berlin Heidelberg, Springer Verlag, 2001; 77-23, Copyright © (2001), with permission from Springer Verlag). Scale bar = 25 μm; in the insertions scale bar = 5 μm.

imaging began. Serial-section electron microscopy of imaged dendritic segments revealed retrospectively that spine sprouting and retraction are associated with synapse formation and elimination. Trimming every other whisker, which induced a rapid and robust remodeling of whisker representation, increased the pool of transient spines present for only a day or less in the cortical representation areas of the trimmed whiskers.[17] Thus, experience-depending plasticity of cortical receptive fields was accompanied by increased synapse turnover. There may, however, be regional differences in the plasticity of dendritic spines. Using a similar *in vivo*-technique in the visual cortex the majority of spines in layer V pyramidal neurons were more stable.[18] Axons and dendrites need guidance for proper orientation, and a number of guidance molecules or surface receptors have been identified. An expression of a common attractant in the neuropil, and activation of its corresponding receptors in axons of one neuron and dendrites of another, might be essential for neuronal network formation during development and plasticity.[19]

As will be exemplified in the following sections, in addition to strengthening contacts between individual neurons, cortical representation areas, ''cortical maps'' can be modified by sensory input, experience, training (Fig. 2)[20] and in response to brain lesions. Synaptic plasticity and number and turnover of dendritic spines in cortical horizontal connections are likely to underlie cortical map reorganization.[21,22] Activity-depending modification of synaptic connection and reorganization of adult cortical areas are thought to involve long-term potentiation (LTP) and long-term depression (LDT), mechanisms by which information is stored in the mammalian central nervous system.[23,24] Despite 30 years research the detailed mechanisms remain unclear.[25] LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites.[26] In a recent study LTP, induced by intracellular electrical micro stimulation, expanded movement representation and induced dendritic hypertrophy in rat sensorimotor cortex.[27] Glutamate, the main excitatory neurotransmitter plays a crucial role, and cortical map reorganization in the primary somatosensory cortex can be prevented by blockade of N-methyl-d-

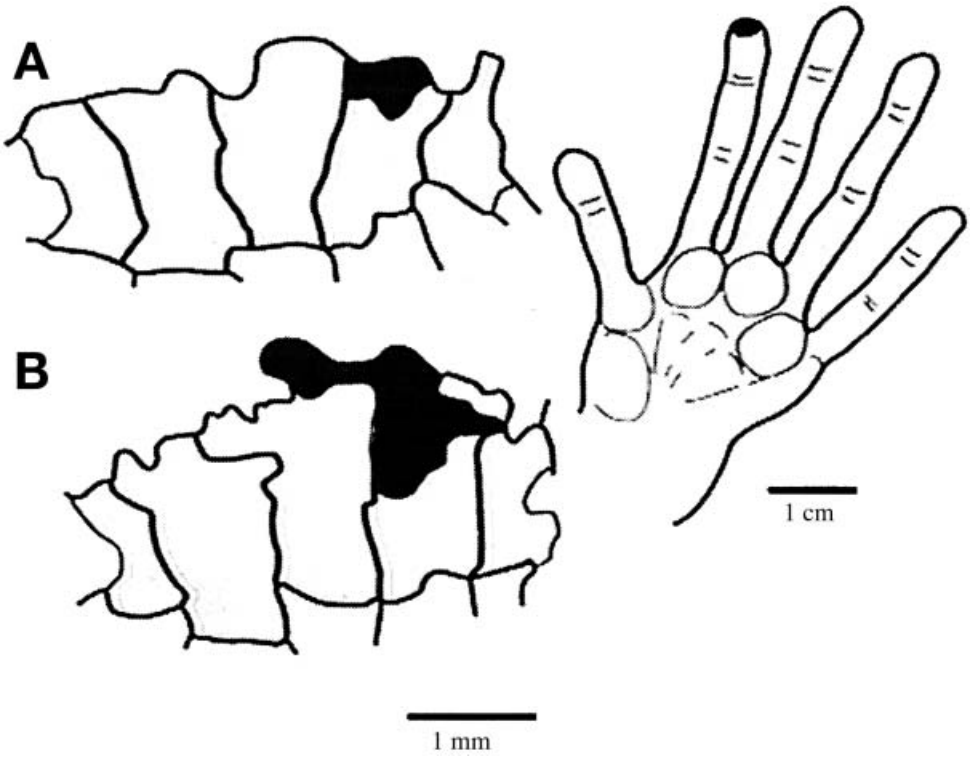


**Fig. 2** The somatosensory cortex of the hand in a monkey before (A) and after (B) repetitive specific tactile stimulation of the tip of the second finger (black areas). (Reproduce from, Jenkins WM, *et al*: J Neurophysiol 1990; 63: 82–104, Copyright © (1990), with permission from The American Physiological Society).

aspartate (NMDA)-receptors. Gamma-aminobutyric acid (GABA)-A receptor antagonists facilitate LTP induction, and the induction can be blocked by GABA-A receptor agonists.[28,29] Also AMPA receptors play an important role.[30] Transmitters released by diffuse neuromodulatory systems that originates in subcortical regions and send long projection axons to the cortex, *i.e.* noradrenalin (locus coeruleus), acetylcholine (nucleus basalis), dopamine (lateral tegmentum), and serotonin (raphe nuclei), can modify the threshold for activity-dependent synaptic plasticity, maybe through a facilitation of NMDA receptor-gated process.[31–34] Another modulator of cerebral cortex synaptic function is nitric oxide[35] that has been shown to interact with dopamine and acetylcholine to induced corticostriatal synaptic plasticity.[36] The molecular mechanisms behind activity-dependent modification of synaptic connections and reorganization of cortex in the adult brain are complex and still not fully understood, and they are likely to differ with the regions studied.[22,37]

Skill learning but not strength training induces cortical reorganization.[38,39] Exercise induces angiogenesis but does not alter movement representations in the cortex.[40] It has recently been reported that cortical synaptogenesis and motor map reorganization occur during late but not early phase of motor skill learning, and that synaptogenesis precedes map reorganization. It was proposed that motor map reorganization and synapse formation do not contribute to the initial acquisition of motor skills but represent the consolidation of motor skill that occurs during late stages of training.[41] There is increasing evidence that non-neuronal cells, in particular astrocytes, have essential roles in plasticity. Astrocytes are responsible for regulating the synaptic environment and for maintaining appropriate levels of neurotransmitters and neurotrophins, and they influence neuronal signaling, number of synapses and play a role in non-synaptic transmission.[42–46]

Neural stem cells, defined by their ability to both self-renew and to differentiate to produce mature progeny cells and neurons, are present in the subventricular zone and in the hippocampus in the adult human brain.[47,48] Animal studies have shown that neurogenesis can be stimulated by many factors including trophic factors, hormones, drugs, environment and brain lesions. Environmental enrichment enhances the survival of newly formed neurons in the hippocampus of intact rats and mice and enhances spatial memory.[49–51]

One important factor restricting brain plasticity after brain lesions is that myelin in the central nervous system contains proteins that inhibit axonal outgrowth.[52,53] The myelin inhibitors share a common receptor and blockage of the receptor promotes CNS

repair and functional recovery.[54] Some promising results with antibodies against this receptor have been reported after spinal and focal brain lesions in animal studies.[55–57]

Interestingly, inosine, a naturally occurring metabolite, has likewise been reported to stimulate axonal growth in the rat corticospinal tract,[58] and to induce axonal rewiring and promote behavioral outcome after focal brain ischemia.[59] It is an important area of research still at the experimental level.

## Neuroimaging Methods Used in the Study of Brain Plasticity

Brain plasticity in the human brain can be studied with several neuroimaging techniques with different temporal and spatial resolution. Thus the temporal resolution varies from minutes in positron emission tomography (PET), seconds in functional magnetic resonance (fMRI) and milliseconds in magnetoencephalography (MEG), which makes MEG best suited for studying temporal spatial patterns of brain activity, that is, where and when the activation starts, and its temporal spread to other regions.[60] Because of the better spatial resolution in fMRI, the wider availability of the technique and the possibility to combine with other MRI techniques, fMRI has been widely used in studies on brain plasticity.[61–63]

Transcranial magnetic stimulation, TMS, is another neurophysiological technique allowing studies of brain functions with a millisecond resolution, which has developed into a popular non-invasive tool for studying the human brain.[64–66] A pulsed magnetic field creates current flow in the brain and can temporarily excite or inhibit synaptic efficiency in specific areas and alter brain function.[64–66] Multiple overlapping motor representations are functionally connected through an extensive horizontal network. By changing the strength of horizontal connections between motor neurons, functionally different neuronal assemblies can form. Delivery of multiple single pulses of TMS does not leave any lasting effect, but repetitive TMS can produce effect that last for some time after the stimulation period. The cortical motor and sensory representations of each hand exert inhibitory influences on the homonymous representation in the opposite hemisphere.[67] Cutaneous anesthesia of the right hand enhances spatial acuity and cortical processing in the left hand,[68] and tourniquet-induced anesthesia of the right hand improves tactile discrimination and grip strength, lasting at least 15 minutes after anesthesia and associated with increased fMRI activation in the right primary motor cortex.[69] Furthermore, repetitive TMS over the left frontal cortex can enhance analogical reasoning,[70] and the encoding of a motor memory in the primary motor cortex can be enhanced by TMS stimulation in healthy volunteers.[71]

## Brain Plasticity in the Development and in the Adult Human Brain

During the early childhood there is a considerable capacity for cross-modal plasticity[72] with redundant connections between auditory and visual areas that gradually decrease between 6 and 36 months of age.[73] Speech processing and auditory localization activate the visual cortex in congenitally blind humans,[74,75] and blind humans localize sound sources better than sighted subjects.[76] Cerebral organization for language functions differs in deaf and hearing subjects, and sign language activates different regions in hearing and deaf signers.[77] The sensorimotor cortical representation of the reading finger is expanded in blind Braille readers[78] and fluctuates with the daily reading activity.[79] Furthermore, tactile acuity is significantly superior in blind subjects, independently of the degree of childhood vision, light perception level, or Braille reading.[80] Linguistic differences have been demonstrated in cortical organization for language in adult individuals with less hemispheric asymmetry in Chinese than in English and Spanish language.[81]

Exposure to musical training in early life shapes the brain, and the brains of musicians have been extensively studied as models of neuroplasticity.[82–84] Pianists have to memorize long and complex bimanual finger sequences, and to translate musical symbols into motor sequences during sight-reading. Long-term motor training and continued practice of complicated bimanual motor activity lead to changes in the brain structure and representation of the brain cortical motor maps. The anterior part of the corpus callosum, consisting of nerve fibers connecting frontal motor-related regions and prefrontal regions crucial for the coordination of bimanual motor activity, is larger in musicians that started musical training before the age of 7 than in musicians without an early start, or in a control population.[85] With diffusion tensor imaging, a technique that allows evaluation of the architecture of the brain white matter, adult subjects with musical training since early childhood differ significantly from control subjects in areas suggesting both cognitive and motor effects of early musical training.[86] Another example is the increased cortical representation of the fingers of the left hand in string players that correlates with the age at which the person had begun to play.[87,88]

Auditory experiences during early postnatal development are important in shaping the functional development of auditory cortical representation, and musicians have increased areas in the auditory cortex for functions important for music such as timbre.[89,90] The

functional anatomy of musical perception, *i.e.* brain activation during a passive music listening task, differs significantly between musicians and non-musicians.[91]

Although the developing brain is clearly more plastic than the adult brain, neuronal connections are continuously remodeled by experience and by performance of specific and complex movements during motor and cognitive learning, and memory processes involve brain plasticity. Rapid and transient alteration of cortical representation areas are seen during learning tasks, most likely related to unmasking of previously existing connections, perhaps as a result of decreased inhibition and increased synaptic efficacy in existing neuronal circuits.[92] Flexible short-term modulations are important in the acquisition of new skills, and can lead to structural changes in the intracortical and subcortical networks as the skill becomes more established and automatic.[93] Even mental practice on a piano keyboard can change the cortical representation of finger flexors and extensor muscles in adult subjects.[94]

Another example of structural plasticity in the adult human brain comes from a study on London taxi drivers, who have a 2-year-long training period in special localization before qualifying as drivers. The volume of gray matter in the right posterior hippocampus, which stores a spatial representation of the environment, is greater than in controls, and the volume increase correlates significantly with the amount of time spent learning to be and practicing as a licensed taxi driver.[95] The failure to find an association between hippocampal volume and navigation expertise in other subjects supports the conclusion that the difference in volume is not an innate genetic difference, but reflect the detail and/or duration of training and use of the spatial representation necessary in the daily work of the drivers.[96]

Examples of the interaction between a dominant gene and environment have been demonstrated in Huntington's disease, a late onset progressive genetic disorder characterized by motor dysfunction, personality and cognitive disturbances leading to dementia and premature death. In a transgenic mice model of Huntington's disease, environmental stimulation significantly delayed the onset of the disease and improved life expectancy.[97–99] In human patients with Huntington's disease the cannabinoid CB1 receptors are lost from the basal ganglia output nuclei prior to the development of other neuropathology,[100] and the improvement during environmental enrichment in an animal model correlated with delayed loss of cannabinoid CB1 receptors.[101] Furthermore, differential clinical and motor control function and different age onset have been reported in pairs of monozygotic twins with Huntington's disease, demonstrating that environmental factors can interact even with dominant genes in humans.[102,103]

## Maladaptive Brain Plasticity

Focal hand dystonia, often called writer's cramp or musician's cramp, is a disabling condition that so far has been very difficult to treat with physiotherapy or other methods. Thus, a recent long-tem outcome study on 21 violin and viola players with focal dystonia an average 13.8 years after onset of symptoms showed that only 38% had been able to maintain their professional careers.[104] Focal hand dystonia is now considered to be a disorder of maladaptive plasticity. In adult monkeys it has been shown that frequent very rapid time-synchronous movements during vigorous practicing can cause a degradation of the sensory feedback controlling fine motor movements, resulting in fusion of the distinct cortical representation of the individual fingers.[105] The abnormal sensory representation interferes with motor control, and abnormal motor control strengthens the sensory abnormality, and the positive feedback loop reinforces the dystonic condition. The sensory representation abnormalities parallel focal hand dystonia in the primate model.[106] Patients with focal hand dystonia have impaired intracortical inhibition and abnormal cortical activations during movements with affected muscles,[107–109] and the regional cerebral blood flow correlates with the severity of symptoms.[110] Compared to control individuals, patients with dystonia have significantly reduced levels of the inhibitory neurotransmitter GABA in the sensorimotor cortex and lentiform nuclei contralateral to the affected hand as demonstrated with *in vivo* magnetic resonance spectroscopy.[111] Based on the hypothesis that successful treatment should be aimed at restoring the normal representation areas of sensory feedback from the hand, methods based on relearning principles have been developed, and substantial improvement has been reported from three centers including a one year follow up study.[112–115] The clinical improvement is associated with altered somatosensory cortical organization.[115] A recent voxel-based morphometry study has demonstrated increase in the gray matter in the hand representation area of primary somatosensory cortex, and to a lesser extent in primary motor cortex in patients compared to controls, suggesting that there might be a hereditary component predisposing for the syndrome.[116]

Embouchure dystonia is a focal task-specific disorder in professional brass and woodwind players involving abnormal non-coordinated movements and involuntary muscle contraction of lip, jaw, and tongue muscles used to control the flow of air into a mouthpiece while playing.[117] It is often so disabling that the musicians have to limit or give up their occupation. There is evidence that abnormal somatosensory reorganization contributes to the disorder.[118] Thus, in a study comparing 8 patients

and 8 control subjects, the patient's digit and thumb representations were shifted in a lateral direction towards the lip representational zone. Furthermore, the patient's upper lip showed decreased sensitivity compared to their lower lips, an asymmetry that was absent in controls.

A strong correlation between the subjective strength of tinnitus and reorganization of the auditory cortex in individuals with hearing loss and tinnitus has led to the proposal that this is another examples of maladaptive plasticity.[119]

## Brain Plasticity due to Lack of Sensory Input to an Intact Brain

Lack of sensory input due to amputation, peripheral nerve lesions or local anesthesia, leads to rapid cortical remodeling with a distorted cortical representation and enlarged and overlapping cortical receptive fields.[120–123] By simultaneous recording of extracellular activity from somatosensory cortex, the thalamus, and trigeminal brainstem area in adult rats, an immediate and simultaneous transient reorganization was produced by subcutaneous lidocain injection, demonstrating that peripheral sensory deafferentation triggers a system-wide reorganization, and that spatiotemporal cortical plasticity is paralleled by subcortical reorganization.[124] Studies on monkeys several years after an amputation have indicated that much of the large-scale cortical reorganization that occurs after a major loss of peripheral inputs reflects the sprouting or expansion of afferents from the remaining forelimb stump into deprived territories of the spinal cord and brain stem. Since the topographic representation of the body is greatly magnified in the cortex, the subcortical changes can result in dramatic cortical map changes.[125,126] Reorganization of the motor efferents to muscles has been demonstrated by a combination of intracortical microstimulation of primary motor cortex and *in vivo* labeling of corticospinal neurons.[127] Stimulation in the deefferented forelimb cortex evoked shoulder stump, trunk and orofacial movements, whereas stimulation in the deefferented hindlimb cortex evoked hip stump, trunk and tail movements. No unresponsive zones were found in the deprived cortex. The reorganization in sensory afferents along with reorganization of the motor efferents to muscles may provide a basis for phantom sensations of movements in the missing forelimb.[126] A recent fMRI study from human amputees indicates that, in addition to primary sensory cortex, somatosensory cortex, thalamus, posterior parietal cortex, and prefrontal cortex may be involved in the phantom sensation.[128] Central maladaptive plasticity has also been proposed to contribute to phantom pain.[129,130] Repetitive transcranial magnetic stimulation of the contralateral parietal cortex can transiently but not lastingly ameliorate phantom limb pain, supporting the hypothesis that phantom pain at least in part is due to a dysfunctional activity in the parietal cortex.[131]

Reconstruction of injured peripheral nerves is a challenging surgical problem. There is no microsurgical technique that makes it possible to reinstate the prelesion axonal connections, and the cortical representation of the reinnervation of the hand will be defragmentated.[132] The axonal growth is slow, and the reinnervation of a hand therefore takes time. Sensory hand training has usually not started until the time reinnervation is taken place. However, because functional reorganization of the cortex occurs rapidly after changes in peripheral input, timing of the onset of sensory-relearning may be critical.[133] A new concept is that sensory relearning programs, aimed at refinement of the distorted receptor fields, should start early to try to normalize the hand map and improve processing at a high-order cortical level. This can be done by taking advantage of the fact that sensory deprivation in one sensory system can have effect of the function of the others due to a continued functional interplay between the different association areas in the adult brain.[72] The hearing sense has a high capacity to discriminate between complex patterns of frequencies, and when touched, individual textures are associated with specific friction sounds. The hypothesis that hearing would be able to take over functions normally devoted to touch after lesions to the hand has led to the development of a Sensor Glove system, which stereophonically transposes the friction sound elicited by active touch. Thus the individual can listen to what the hand is touching and the training can be initiated before the reinnervation of the hand takes place. Preliminary results from a prospective clinical randomized study indicate that use of this re-learning system improves recovery of tactile discrimination in the nerve-injured hand (132).

## Lesion-induced and Training Induced Brain Plasticity

Despite permanent tissue loss most surviving stroke patients regain some function with time. In 1973 a neuroanatomist wrote in a paper based on his own experience after a stroke ''since regeneration of transectioned central axons has never been convincingly demonstrated in higher mammals, it seems that one must resort to the assumption that intact fibers take over from the damaged ones''.[134] That is indeed the case and many molecular and neurophysiological mechanisms have been proposed to take part in lesion-induced brain plasticity.[66,135–142]

That reorganization of cortical representation after brain injury could be the neurophysiological model of

the bases of recovery from cortical lesions was first suggested by Jenkins and Merzernich,[143] a hypothesis that has been supported by many later studies. A lesion to a small portion of the cortical motor hand representation in monkeys results in a further loss of hand territory in the adjacent undamaged cortex. Retraining of skilled hand use improves behavioral recovery and prevents tissue loss, and the hand representation may expand into regions formerly occupied by representationsof the elbow and shoulder.[144] Similarly, cortical reorganization of primary somatosensory cortex is associated with sensorimotor skill recovery after cortical lesions in adult monkeys,[145] and cortical reorganization induced by motor learning is associated with synaptogenesis.[146]

The spontaneous postischemic functional improvement after an ischemic infarct in the hand representation area of primary motor cortex has been studied in monkeys.[147] An initial post infarct motor impairment of the contralateral hand was followed by a gradual improvement over three months. Intracortical microstimulation mapping at 12 weeks revealed substantial enlargement of the hand representation in the ventral premotor cortex remote from the lesion. The enlargement was proportional to the amount of hand representation destroyed, that is the greater the damage to intracortical pathways, the greater the plasticity in intact areas.[147]

In addition to training-induced alteration in cortical maps, there is evidence that the post-ischemic environment can influence functional outcome after brain lesions.[148–151] Thus, environmental enrichment improves functional outcome after experimental brain infarcts,[152,153] increases the number of dendritic spines,[9] alters gene expression pattern,[154,155] influences the lesion-induced progenitor cell differentiation[156] augments the effect of training,[157] and interacts with drug treatment.[158] Furthermore, it enhances the efficacy of neocortical transplantation.[159,160] Similar results have been obtained after striatal transplantation in animal models of Parkinson's disease.[161]

The mechanisms that mediate functional recovery after stroke may differ depending on time after the stroke, lesion site and degree of recovery.[137,139,140,162] A controversial question has been to what extent changes in the intact hemisphere are responsible for good outcome in human stroke patients. Early PET studies on blood flow distribution during finger movements in a previously paretic hand demonstrated complex patterns of activation with multiple areas of increased activation on both sides, and with large individual variations.[163,164] Later studies with fMRI suggest that the activation in intact regions in the lesioned hemisphere is most closely related to good recovery in human patients.[165–168] Thus, Carey *et al.*,[165] who studied the effect of training several years after stroke onset, demonstrated a shift of activation from the intact to the lesion side in connection with improved function. A comparison between patients with poor and good recovery indicated that patients with poor recovery were more likely to recruit a number of motor-related brain regions during a motor task, whereas patients with more complete recovery were likely to have a task-related brain activation that were more similar to control subjects with no stroke.[166] Likewise, results from studies evaluating the effect of transcranial magnetic stimulation on motor performance of the paretic hand of chronic stroke patients indicated that recovered function in a paretic hand of chronic stroke patients relies predominantly on reorganized activity within sensorimotor regions in the affected hemisphere.[169–171] However, it has been proposed that in some patients with subcortical lesions and severe damage to the corticospinal tract, a slow recovery might be obtained by the utilization of the intact contralateral sensorimotor cortices.[172]

Thus most data today indicate that the substrate for improved functional recovery is mainly in regions ipsilateral to the lesion, and that high activity in the intact hemisphere is connected with less good recovery. In agreement with the concept of inter-hemispheric inhibition described earlier,[67–69] the primary motor cortex of the intact hemisphere could influence functional recovery through trans-callosal connections. Interestingly, a very recent study indicated an abnormally high inter-hemispheric inhibitory drive from the intact to the affected hemisphere during voluntary movement by the paretic hand.[173] The authors commented that it is conceivable that this abnormality could adversely influence motor recovery in some patients with subcortical stroke, clearly an issue for future investigations. If so, it would be expected that transient deafferentation of the intact side[67–69] would improve the motor function on the weak side.

Basic research on brain plasticity has lead to introduction of new techniques in neurorehabilitation. One such method, based on extensive studies in monkeys by Taub and coworkers, is constraint-induced training.[174–175] Already in 1940 it was observed that monkeys with lesions to one pyramidal tracts failed to use the affected limb, and that the use of the weak limb could be improved if the unaffected limb was restrained.[176] By preventing the patients from using the healthy arm and hand and thus intensify the training, together with what the authors call shaping that includes making a task successively more difficult, the cortical representation maps can change together with improved performance.[177–178] The major part of the effect is probably caused by the intense training and the relative importance of preventing movement in the intact hand is unclear.[179] A multisite randomized trial to

evaluate the therapeutic success, the influence of post-stroke time before starting the training, and the persistence of any effect over 2 years, is ongoing in the USA.[180] Good effects have been obtained also with techniques such as training with robots that do not require any immobilization of the intact side.[181–185] The intensity of the training seems to be a crucial factor in the studies reported beneficial effects of specific training.

Training with a mirror is another interesting approach. Arm amputees can experience the perception of movement of a phantom limb while looking at a mirror reflection of the moving, intact arm superimposed on the perceived phantom. To provide illusory visual feedback of movement such use of a mirror has been tried in rehabilitation of hemiparetic patients.[186–187] Theoretically this method is interesting in light of current knowledge of the so-called mirror neuron system. Seeing a purposeful action activates neurons in the prefrontal regions that are activated both by performing and observation of purposeful actions,[188–190] neurons that have connections with many regions of the brain and are thought to be essential for the human capacity to imitate and understand other persons intention. Virtual reality is another technique that is under evaluation.[191] Mental training activates most of the same circuitry in the brain as real action does,[94,192] and mental practice is another method preliminary reported to be of value.[193]

Cognitive deficiencies are common among stroke patients and memory problems, attention and ability to concentrate are likely to influence all training. Thus, the effect of mental practice after stroke is related to the working memory capacity of the patients.[194] Most stoke patients have better function in the shoulder and upper arm than in the hand. Since there is competition among body parts for territory in the sensorimotor cortex (Fig. 2), reducing the sensory input from surrounding areas by transient deafferentation of the upper arm during hand motor practice dramatically improved hand motor function, including some activities of daily living.[195]

It should be stressed that few of these new techniques have been properly evaluated in larger clinical studies yet. However, the promising neurobiological research is changing the attitude to neurorehabilitation. Collaboration between basic and applied science will continue to be important for further progress. Most of the spontaneous functional sensorimotor improvement occurs within the first 3–6 months after a stroke, and that is the optimal time for rehabilitation. However, specific training can alter cortical representation areas even years after stroke.[165] An important aspect is that training has to be continued to keep up functional gains. Clinical studies indicate that the patient's attitude, activities and social interaction influence functional outcome and quality of life after brain lesions. Rehabilitation strategies that are meaningful for the individual patient are likely to be the most effective.[150]

Additional ways of enhancing brain plasticity is being tested in animals, including the trials to find ways to enhance axonal outgrowth mentioned in the introduction.[52–59] Another area of great interest is whether lesion-induced stem cell proliferation can have beneficial effects after brain lesions. As demonstrated by several recent reviews,[196–199] many studies have shown a marked increase in stem cell/progenitor cell proliferation in hippocampus and the subventricular zone after global and focal brain ischemia. That endogenous neural precursors can be induced to differentiate into mature neurons in adult mammalian neocortex and form long-distance cortico-thalamic and cortico-cortico connections has been shown in a model of apoptotic selective death of cortical pyramidal neurons.[200,201] In another model of selective neuronal death, global ischemia, intraventricular infusion of FGF-2 and epidermal growth factor (EGF) during 4 days markedly increased regeneration of hippocampal pyramidal neurons with electrophysiological evidence that the neurons were integrated into the existing brain circuitry, and it was proposed that the new cells contributed to the amelioration of neurological deficits observed in the treated rats.[202] After focal brain ischemia, proliferating cells from the subventricular zone migrate to the striatum after large striato-cortical lesions induced by a transient MCA occlusion, a small part of which may develop into medium sized striatal neurons.[203,204] However, no study has so far demonstrated integration into neuronal circuits or functional effects of neurogenesis after focal brain ischemia. It is possible that cell or tissue transplantation may be more successful, an issue with many aspects that will not be dealt with here.

## Aging and Brain Plasticity

To what extent environmental factors can influence the aging processes is controversial. In experimental animals, environmental and social interactions can partially offset age-related decrease and fragmentation of the somatosensory cortical maps.[205] 14 days of exposure to an enriched environment in 28-month-old mice significantly enhanced spatial memory and synaptophysin levels in hippocampus and frontoparietal cortex.[206] Mice living in an enriched environment from the age of 10 to 20 months had a fivefold higher hippocampal neurogenesis together with significantly better learning ability and exploratory behavior than control rats in a standard environment.[207] Twin studies have shown that brain volume, the size of corpus callosum and the size of the ventricles are highly genetically deter-

mined whereas more variability has been found in the gyral and sulcal patterns.[208–210] In a large twin study about 60% of the variance of the temporal horns and 80% of the variance of corpus callosum were considered to be attributable to genetic components compared to 40% of the variance of hippocampal volume, suggesting that the environment or gene-environmental interactions have greater control in modifying hippcampal size,[211] a conclusion that is consistent with results from an MRI study of hippocampus in monozygotic twins with discordant cognitive abilities.[212]

Studies with PET and fMRI indicate that elderly people activate more regions than younger even for simple motor task, with no difference in accuracy but increase in reaction time and greater activation in the same areas as activated in the young, and with recruitment of additional cortical and subcortical areas.[213–215] It has been interpreted to support the notion that an adaptable and plastic motor network is able to respond to age related structural and neurochemical changes in order to maintain performance levels.[214,215] In an episodic memory-encoding task older adults engaged much of the same neural circuitry as younger subjects. In addition, age-related differences in prefrontal and temporal activity were observed during successful episodic encoding. One difference was a bilateral activity in prefrontal regions in the older subjects compared to a left activation in young.[216] More bilateral patterns of prefrontal activity in older adults than in younger adults have also been shown during working memory and visual attention tasks, suggesting that older adults may use selective compensatory mechanisms in processing information.[217]

The effect of practice and of cognitive ageing has been studied in a large longitudinal study of elderly community residents in the UK.[218] Age-related changes were relatively slight between 49 and 70 years and much more marked between 70 and 80 years. However, the population average effect of practice was large relative to the age-related change, and the variation between individuals increased with age. This study provided significant empirical evidence that individuals age at markedly different rates. A large population-based studies of older persons in the USA in a model that controlled for baseline level of cognition, age, sex, race and education, demonstrated that frequent participation in cognitively stimulating activities was associated with significantly reduced cognitive decline in older persons, an effect that remained when the investigators controlled for depressive symptoms and chronic medical conditions.[219] Furthermore, frequent participation of cognitive stimulating activities appeared to be associated with reduced risk for Alzheimer's disease.[220,221]

Aging is accompanied by a decline in muscle strength and ability to maintain submaximal force. However, skilled finger movement training improves the ability to control submaximal pinch force, hand steadiness and manual speed also in elderly individuals.[222] An investigation with magnetic resonance spectroscopy in different brain regions before and after 5 weeks of memory training in healthy elderly showed that memory improvement was accompanied by elevation of creatine and choline signals in the hippocampus. Interestingly, those considered to be at risk for neuronal dysfunction because of low neurometabolites at baseline demonstrated the largest increases after training.[223]

A Finnish study in which the participants were grouped according to their own identification with age suggested an association between perceptions of personal aging and physical and psychological well being.[224] Another study on Swedish and Canadian samples of older adults suggested that subjective health should be added to the growing number of individual-different variable that are predictive of episodic memory change in very old age.[225] Together with the recent demonstrations on neurobiological effects of expectation, including activation of endorphin pathways in individuals with pain[226] metabolic activation pattern in depression[227] and dopamine release in Parkinson's disease,[228] the data suggest that individual variations in self-confidence, expectation and attitude towards life events, in addition to genetic factors, may help in explaining the larger inter-individual variations in cognitive performance with increasing age.[218] Remarkable achievements in the graphic arts, architecture and music have often been accomplished in later life,[229,230] and as mentioned above, the cognitive variance between individuals at high age is large. Creativity may vary with the specific field evaluated[231] or change rather than decline with age.[232] In an extensive sample of more than 1,900 works by 172 classical composers, Simonton compared their last works, ''swan songs'', with their earlier work as to melodic originality, melodic variation, repertoire popularity, aesthetic significance, listener accessibility, performance duration, and thematic size. The composers' swan songs tended to score lower in melodic originality and performance but higher in repertoire popularity and aesthetic significance.[233]

There are many anecdotal reports that performing musicians and conductors live long and active lives. Legendary conductors like Arturo Toscanini, Leopold Stokowski and Arthur Fiedler have had long and productive careers that has led to the proposal that symphony conductors are a remarkably long-lived group. In a 20-year follow study of 437 active and former conductors of major regional and community symphony and opera orchestras in the United States, published in

the Statistical Bulletin in the US[234] the over all mortality was 38% lower than in the general population with the largest difference (56%) in the 50–59 age range and a 34% reduction in the ages 80 and over. However, it was pointed out that the results on conductors parallel the results of a study demonstrating that the mortality among top corporative executives was much more favorable than the mortality among business executive at all levels of accomplishment in the USA. The conclusion was that the data support the theory that work fulfillment and worldwide recognition of professional accomplishments are important determinants of health and longevity. One personal experience from Japan is that I was present when Asahina Takashi, then 91, conducted the Japan New Philharmonic orchestra in the Sumida Triphony Hall in Tokyo in 1999, an excellent performance that got very long and enthusiastic ovations.

Like conductors, many legendary pianists have performed high up in the ages. The degree of skill maintenance for older expert pianists is predicted by the amount of practice.[235] In a study comparing older expert and amateur pianists both groups showed the normal pattern of age-related reductions in standard measures for general processing speed. Whereas performance on music-related tasks showed similar age-graded decline for amateur pianists, the average performance level for the expert pianists was only slightly below that of young expert pianists.[235] When pianists of a wide experience and age range were tested on measures of musical memory and musical perceptual speed, the results indicated that high levels of experience in the older participants partially attenuated the negative effects of age on the memory and speed tasks.[236]

Studies on longevity in the population in Okinawa are in agreement with the concept that genetic factors interact with life style, self-confidence and social networks, as well as with diet.[237,238] The Japanese twins, Kin san and Gin san, who if I am correctly informed became famous after singing in the Japanese TV at the age of 100, were seen in international newspapers at the age of 107 when Gin-san, apparently the most active of the two that lived a little longer, was planting a tree while the sister was looking on sitting in a wheelchair. That is to me an excellent example that old individuals can still enjoy life and that in spite of the same genes there might be some differences that can be influenced by attitude and activities.

## Concluding Remarks

Our brain is continuously changing and it is important what we do and what we think. A healthy brain can form new dendrites, spines and synapses throughout our lifetime even if we need to activate more neural circuits for specific tasks than when we were young. Brain damage is still and will remain a serious problem. However, current basic and clinical data indicate that the possibilities to stimulate brain plasticity after a lesion are larger than earlier believed, and the progress made in neurorehabilitation is promising. The concept on brain plasticity has wide implication also for areas outside neuroscience such as hand surgery.[132,133] For the first time is seems that we have ways to successfully treat focal hand dystonia.[112–115] We cannot prevent aging but the way we live out lives may influence the aging process. That the environment and our activities influence our lives is basic human knowledge; what is new is that we are starting to understand a little of how it happens.

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